```
=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 15:31:28 ON 26 OCT 2001
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2001 AMERICAN CHEMICAL SOCIETY (ACS)
```



```
FILE COVERS 1947 - 26 Oct 2001  VOL 135 ISS 19
FILE LAST UPDATED: 25 Oct 2001  (20011025/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

 This file supports REG1stRY for direct browsing and searching of
 all substance data from the REGISTRY file.  Enter HELP FIRST for
 more information.

HCAplus now provides online access to patents and literature covered
in CA from 1947 to the present.  On April 22, 2001, bibliographic
information and abstracts were added for over 2.2 million references
published in CA from 1947 to 1966.


=>
=>

=> d stat que l24
L23           41 SEA FILE=REGISTRY ABB=ON  PLU=ON  (FQW'AAA'VGHL)/SQEP OR
                 (FQW'AIB'VGHI)/SQEP OR (FQW'AIB'VGHL)/SQEP OR (FQWAV'AIB'HI)/SQ
                 EP OR (FQWAV'AIB'HL)/SQEP OR (FQWAVGHL)/SQEP
L24           46 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L23


=>
=>

=> d ibib abs hitrn l24 1-46

L24  ANSWER 1 OF 46  HCAPLUS  COPYRIGHT 2001 ACS
ACCESSION NUMBER:         2001:636087  HCAPLUS
DOCUMENT NUMBER:          135:190403
TITLE:                    Synthesis of bombesin peptide analogs and their uses
                          in treatment of cancer
INVENTOR(S):              Burman, Anand C.; Prasad, Sudhanan; Mukherjee, Rama;
                          Jaggi, Manu; Singh, Anu T.; Mathur, Archna
PATENT ASSIGNEE(S):       Dabur Research Foundation, India
SOURCE:                   PCT Int. Appl., 35 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.       KIND  DATE          APPLICATION NO.  DATE
```

WO 2001062777	A1	20010830	WO 2000-US20873	20000731

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: IN 2000-DE147 A 20000224

OTHER SOURCE(S): MARPAT 135:190403

AB The invention discloses sequences of novel peptides that are antagonists to bombesin and bombesin like peptides and their uses in the treatment of cancer. The invention particularly relates to the design and synthesis of the novel peptides incorporating .alpha.,.alpha.-amino acids in a site specific manner. The invention also provides methods for the generation of these peptides, compns. contg. the peptides and the pharmacol. applications of these peptides esp. in the treatment and prevention of cancer.

IT **357175-68-9P 357175-69-0P 357175-71-4P 357175-80-5P 357176-08-0P 357176-55-7P 357176-70-6P 357176-83-1P**

RL: BAC (Biological activity or effector, except adverse); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino acid sequence; synthesis of bombesin peptide analogs and their uses in treatment of cancer)

REFERENCE COUNT: 4

REFERENCE(S):
(1) Dabur Research Foundation; WO 0047221 A 2000 HCAPLUS
(2) Ici Plc; EP 0315367 A 1989 HCAPLUS
(3) Ici Plc; EP 0345990 A 1989 HCAPLUS
(4) Merrell Dow Pharma; EP 0468497 A 1992 HCAPLUS

L24 ANSWER 2 OF 46 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:824291 HCAPLUS

DOCUMENT NUMBER: 134:21425

TITLE: Protection of endogenous therapeutic peptides from peptidase activity through conjugation to blood components

INVENTOR(S): Bridon, Dominique P.; Ezrin, Alan M.; Milner, Peter G.; Holmes, Darren L.; Thibaudeau, Karen

PATENT ASSIGNEE(S): Conjuchem, Inc., Can.

SOURCE: PCT Int. Appl., 733 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000069900	A2	20001123	WO 2000-US13576	20000517
WO 2000069900	A3	20010215		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,

MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,
SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

WO 2000070665 A2 20001123 WO 2000-IB763 20000517
WO 2000070665 A3 20010419
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,
CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,
SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ,
MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML,
MR, NE, SN, TD, TG

EP 1105409 A2 20010613 EP 2000-936023 20000517
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO

PRIORITY APPLN. INFO.: US 1999-134406 P 19990517
US 1999-153406 P 19990910
US 1999-159783 P 19991015
WO 2000-US13576 W 20000517

AB A method for protecting a peptide from peptidase activity in vivo, the peptide being composed of between 2 and 50 amino acids and having a C-terminus and an N-terminus and a C-terminus amino acid and an N-terminus amino acid is described. In the first step of the method, the peptide is modified by attaching a reactive group to the C-terminus amino acid, to the N-terminus amino acid, or to an amino acid located between the N-terminus and the C-terminus, such that the modified peptide is capable of forming a covalent bond in vivo with a reactive functionality on a blood component. The solid phase peptide synthesis of a no. of derivs. with 3-maleimidopropionic acid (3-MPA) is described. In the next step, a covalent bond is formed between the reactive group and a reactive functionality on a blood component to form a peptide-blood component conjugate, thereby protecting said peptide from peptidase activity. The final step of the method involves the analyzing of the stability of the peptide-blood component conjugate to assess the protection of the peptide from peptidase activity. Thus, the percentage of a K5 kringle peptide (Pro-Arg-Lys-Leu-Tyr-Asp-Lys-NH2) conjugated to human serum albumin via MPA remained relatively const. through a 24-h plasma assay in contrast to unmodified K5 which decreased to 9% of the original amt. of K5 in only 4 h in plasma.

IT **309246-58-0**
RL: PRP (Properties)
(unclaimed sequence; protection of endogenous therapeutic peptides from peptidase activity through conjugation to blood components)

L24 ANSWER 3 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:573679 HCAPLUS
DOCUMENT NUMBER: 133:198647
TITLE: Antiangiogenic drugs
INVENTOR(S): Mukherjee, Rama; Jaggi, Manu; Prasad, Sudhanand; Burman, Anand C.; Rajendran, Praveen; Mathur, Archana; Singh, Anu T.
PATENT ASSIGNEE(S): National Institute of Immunology, India; Dabur Research Foundation; Cord, Janet, I.
SOURCE: PCT Int. Appl., 42 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000047221	A1	20000817	WO 2000-US3559	20000211

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-248381 A1 19990211

AB The invention relates to the use of peptides individually or in combination, for treating and/or preventing angiogenesis. It also relates to the use of peptide analogs or a combination of peptides referred to as MuJ-7 as anticancer drugs in restricting tumor growth and spread by inhibiting tumor angiogenesis. MuJ-7, in addn. inhibits metastasis through its antiangiogenic activity in all cancers. The invention also relates to a pharmaceutical compn. contg. either individual peptides or in combination, and methods of treatment of human beings and animals for curing and/or preventing angiogenesis.

IT **124199-90-2 288570-83-2 288570-85-4 288570-87-6 288570-89-8**
RL: BAC (Biological activity or effector, except adverse); PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(antitumor antiangiogenic peptides)

REFERENCE COUNT: 8
REFERENCE(S):
(1) Bogden; US 5217955 A 1993 HCAPLUS
(2) Coy; US 5410019 A 1995 HCAPLUS
(4) Gozes; US 5565424 A 1996 HCAPLUS
(5) Hanahan; Cell 1996, V86, P353 HCAPLUS
(6) Kim; US 5552520 A 1996 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 4 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:289509 HCAPLUS
DOCUMENT NUMBER: 133:105330
TITLE: The utilization of [18F]N-succinimidyl 4-fluorobenzoate ([18F]SFB) for labeling bombesin derivatives
AUTHOR(S): Scheunemann, M.; Mading, P.; Bergmann, R.; Steinbach, J.; Johannsen, B.
CORPORATE SOURCE: Germany
SOURCE: Wiss.-Tech. Ber. - Forschungszent. Rossendorf (1999), FZR-283, 61-62
CODEN: WBFRFQ; ISSN: 1437-322X
DOCUMENT TYPE: Report
LANGUAGE: English

AB Using [18F]-labeled succinimidyl 4-fluorobenzoate, the labeled fluorobenzoyl group was introduced to the N-terminus of peptides, H-Phe-Gln-Gly-Pro-OH and H-D-Phe-Gln-Trp-Ala-Val-Gly-His-Leu-NHEt.

Specific radioactivity of the labeled peptides were measured.

IT **283178-52-9P**
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and radioactive decay of [18F]-labeled bombesin derivs.)

IT **283178-50-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of bombesin derivs.)

REFERENCE COUNT: 7
REFERENCE(S):
(2) Carney, D; Cancer Research 1987, V47, P821 HCAPLUS
(4) Kroog, G; Med Res Rev 1995, V15, P389 HCAPLUS
(5) Moody, T; Science 1981, V214, P1246 HCAPLUS
(6) Scheunemann, M; Report January 1998-June 1999, Institute of Bioinorganic and Radiopharmaceutical Chemistry 1999, FZR-270, P26 HCAPLUS
(7) Wester, H; Nucl Med Biol 1996, V23, P365 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 5 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:475113 HCAPLUS
DOCUMENT NUMBER: 131:243570
TITLE: Syntheses and biological activities of potent bombesin receptor antagonists
AUTHOR(S): Llinares, M.; Devin, C.; Chaloin, O.; Azay, J.; Noel-Artis, A.-M.; Bernad, N.; Fehrentz, J.-A.; Martinez, J.
CORPORATE SOURCE: Laboratoire des Amino-acides, Peptides et Proteines, UMR 5810, CNRS-Universites Montpellier I and II, Faculte de Pharmacie, Montpellier, 34060, Fr.
SOURCE: J. Pept. Res. (1999), 53(3), 275-283
CODEN: JPERFA; ISSN: 1397-002X
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Bombesin receptor antagonists are potential therapeutic agents due to their ability to act as inhibitors of cellular proliferation. On the basis of our hypothesis concerning the mechanism of action of gastrin assocg. an activating enzyme to the receptor and on the results reported in the literature, we have synthesized bombesin analogs which have been modified in the C-terminal part. Potent bombesin receptor antagonists were obtained by replacement of Leu-13 with a statyl residue or with a residue bearing an hydroxyl group in place of the carbonyl function of Leu-13. Several inhibitors were able to recognize the bombesin receptor on rat pancreatic acini and antagonized bombesin stimulated amylase secretion in the nano-molar range. These compds. were also able to recognize the bombesin receptor and to inhibit [3H] thymidine incorporation in 3T3 cells with the same potency.

IT **244168-25-0**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(biol. activity of as bombesin receptor antagonists)

REFERENCE COUNT: 28
REFERENCE(S):
(1) Anastasi, A; Experientia 1971, V27, P166 HCAPLUS
(2) Castro, B; Tetrahedron Lett 1975, P1219 HCAPLUS
(3) Ceska, M; Clin Chim Acta 1969, V26, P437 HCAPLUS
(4) Coy, D; J Biol Chem 1988, V263, P5056 HCAPLUS
(6) Dubreuil, P; Peptides 1990 1991, P712 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 6 OF 46 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:407854 HCAPLUS
DOCUMENT NUMBER: 131:179925
TITLE: An Aspartate Residue at the Extracellular Boundary of TMII and an Arginine Residue in TMVII of the Gastrin-Releasing Peptide Receptor Interact To Facilitate Heterotrimeric G Protein Coupling
AUTHOR(S): Donohue, Patrick J.; Sainz, Eduardo; Akeson, Mark; Kroog, Glenn S.; Mantey, Samuel A.; Battey, James F.; Jensen, Robert T.; Northup, John K.
CORPORATE SOURCE: Laboratories of Molecular Biology and Cellular Biology, National Institute on Deafness and Other Communication Disorders National Institutes of Health, Rockville, MD, 20850, USA
SOURCE: Biochemistry (1999), 38(29), 9366-9372
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mammalian bombesin receptor subfamily of G protein-coupled receptors currently consists of the gastrin-releasing peptide receptor (GRP-R), neuromedin B receptor, and bombesin receptor subtype 3. All three receptors contain a conserved aspartate residue (D98) at the extracellular boundary of transmembrane domain II and a conserved arginine residue (R309) near the extracellular boundary of transmembrane domain VII. To evaluate the functional role of these residues, site-directed GRP-R mutants were expressed in fibroblasts and assayed for their ability to both bind agonist and catalyze exchange of guanine nucleotides. Alanine substitution at GRP-R position 98 or 309 reduced agonist binding affinity by 24- and 56-fold, resp., compared to wild-type GRP-R. Single swap GRP-R mutations either resulted in no receptor expression in the membrane (D98R) or the protein was not able to bind agonist (R309D). In contrast, the double swap mutation (D98R/R309D) had high-affinity agonist binding, reduced from wild-type GRP-R by only 6-fold. In situ reconstitution of urea-extd. membranes expressing either wild-type or mutant (D98A or R309A) GRP-R with Gq indicated that alanine substitution greatly reduced G protein catalytic exchange compared to wild-type GRP-R. The D98R/R309D GRP-R had both a higher intrinsic basal activity and a higher overall catalytic exchange activity compared to wild-type; however, the wild-type GRP-R produced a larger agonist-stimulated response relative to the double swap mutant. Taken together, these data show that GRP-R residues D98 and R309 are crit. for efficient coupling of GRP-R to Gq. Furthermore, our findings are consistent with a salt bridge interaction between these two polar and oppositely charged amino acids that maintains the proper receptor conformation necessary to interact with G proteins.

IT **130800-38-3**, 6-13-[D-Phe6]-Bombesin methyl ester
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(gastrin-releasing peptide receptor transmembrane domain II aspartate residue and transmembrane domain VII arginine residue interaction to facilitate heterotrimeric Gq protein coupling)

REFERENCE COUNT: 39
REFERENCE(S):
(1) Akeson, M; J Biol Chem 1997, V272, P17405 HCAPLUS
(2) Baldwin, J; Curr Opin Cell Biol 1994, V6, P180 HCAPLUS
(3) Battey, J; Proc Natl Acad Sci U S A 1991, V88, P395 HCAPLUS
(4) Benya, R; Mol Pharmacol 1992, V42, P1058 HCAPLUS
(5) Benya, R; Mol Pharmacol 1994, V46, P235 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 7 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:288456 HCAPLUS
DOCUMENT NUMBER: 131:45089
TITLE: Synthesis and biological evaluation of C-terminal hydroxamide analogues of bombesin
AUTHOR(S): Devin, Chantal; Bernad, Nicole; Cristau, Michele; Artis-Noel, Anne-Marie; Heitz, Annie; Fehrentz, Jean-Alain; Martinez, Jean
CORPORATE SOURCE: Laboratoire des Amino-acides, Peptides et Proteines (LAPP), Faculte de Pharmacie, Montpellier, 34060, Fr.
SOURCE: J. Pept. Sci. (1999), 5(4), 176-184
CODEN: JPSIEI; ISSN: 1075-2617
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This work reports the synthesis of two octapeptide analogs of bombesin in which the C-terminal methionine amide residue has been replaced by benzyl-protected hydroxylamine, H-D-Phe-Gln-Trp-Ala-Val-Gly-His-Leu-NHOBzl (1), and replaced by hydroxylamine, H-D-Phe-Gln-Trp-Ala-Val-Gly-His-Leu-NHOH (2). These peptides were tested for their ability to recognize the bombesin receptor on rat pancreatic acini and on 3T3 cells, to stimulate (i) amylase secretion from rat pancreatic acini and (ii) accumulation of tritiated thymidine in 3T3 cells. Peptides 1 and 2 were able to recognize bombesin receptors on both models with high affinity (Ki = 7 .+-. 2 and 5.8 .+-. 0.9 nM on rat pancreatic acini, and Ki = 4.1 .+-. 1.2 and 7.7 .+-. 1.9 nM on 3T3 cells, resp.). Interestingly, 1 behaved as a potent agonist in stimulating amylase secretion from rat pancreatic acini and was able to stimulate thymidine accumulation in 3T3 cells. Whereas, 2 was able to potently antagonize bombesin-stimulated amylase secretion (Ki = 22 .+-. 5 nM) in rat pancreatic acini and had no proper effect on 3T3 cells; however, it was able to inhibit bombesin-stimulated thymidine accumulation in 3T3 cells with high potency (Ki = 1.6 .+-. 0.6 nM).
IT **215532-61-9P**
RL: BAC (Biological activity or effector, except adverse); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and biol. evaluation of C-terminal hydroxamide analogs of bombesin)
IT **215532-60-8P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and biol. evaluation of C-terminal hydroxamide analogs of bombesin)
IT **227624-59-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(synthesis and biol. evaluation of C-terminal hydroxamide analogs of bombesin)
REFERENCE COUNT: 18
REFERENCE(S): (1) Anastasi, A; Experientia 1971, V27, P166 HCAPLUS
(2) Cai, R; Proc Natl Acad Sci USA 1994, V91, P12664 HCAPLUS
(3) Ceska, M; Clin Chim Acta 1969, V26, P437 HCAPLUS
(4) Coy, D; J Biol Chem 1988, V263, P5056 HCAPLUS
(6) Gardner, J; J Physiol 1977, V270, P439 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 8 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:286794 HCAPLUS
DOCUMENT NUMBER: 131:83232
TITLE: Pharmacology and cell Biology of the bombesin receptor

subtype 4 (BB4-R)

AUTHOR(S): Katsuno, Tatsuro; Pradhan, Tapas K.; Ryan, Richard R.; Mantey, Samuel A.; Hou, Wei; Donohue, Patrick J.; Akeson, Mark A.; Spindel, Eliot R.; Battey, James F.; Coy, David H.; Jensen, Robert T.

CORPORATE SOURCE: Digestive Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases National Institutes of Health, Bethesda, MD, 20892, USA

SOURCE: Biochemistry (1999), 38(22), 7307-7320
CODEN: BICHAW; ISSN: 0006-2960

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Recently, a fourth member of the bombesin (Bn) receptor family (fBB4-R) was isolated from a cDNA library from the brain of the frog, Bombina orientalis. Its pharmacol. and cell biol. are largely unknown, and no known natural cell lines or tissues possess sufficient nos. of fBB4-R's to allow either of these to be detd. To address these issues, the authors have used three different strategies. FBB4-R expression in cells widely used for other Bn receptor subtypes was unsuccessful as was expression in two frog cell lines. However, stable fBB4-R cell lines were obtained in CHO-K1 cells which were shown to faithfully demonstrate the correct pharmacol. of the related Bn receptor, the GRP receptor, when expressed in these cells. [DPhe6,.beta.Ala11,Phe13,Nle14]Bn(6-14) was found to have high affinity (Ki = 0.4 nM) for the fBB4 receptor and 125I-[DTyr6,.beta.ala11,Phe13,Nle14]Bn(6-14) to be an excellent ligand for this receptor. The fBB4-R had a unique pharmacol. for naturally occurring Bn-related agonists, with the presence of a penultimate phenylalanine being crit. for high-affinity interaction. It also had a unique profile for six classes of Bn antagonists. The fBB4-R was coupled to phospholipase C with activation increasing [3H]inositol phosphates and mobilizing Ca2+ almost entirely from cellular sources. There was a close correlation between agonist the receptor occupation and the receptor activation. Three of the five classes of Bn receptor antagonists that interacted with higher affinity with the fBB4-R functioned as fBB4-R antagonists and two as partial agonists. FBB4-R activation stimulated increases in phospholipase D (PLD) over the same range of concns. at which it activated phospholipase C. These results demonstrate that the fBB4 receptor has a unique pharmacol. for agonists and antagonists and is coupled to phospholipase C and D. The availability of these cell lines, this novel ligand, and the identification of three classes of antagonists that can be used as lead compds. should facilitate the further investigation of the pharmacol. and cell biol. of the BB4 receptor.

IT **124176-07-4 124199-91-3 130800-28-1**
130800-37-2 130800-38-3 229626-64-6
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(pharmacol. and cell biol. of bombesin receptor subtype 4 in relation to different agonist and antagonist characterization)

REFERENCE COUNT: 40

REFERENCE(S):
(1) Battey, J; Proc Natl Acad Sci USA 1991, V88, P395 HCAPLUS
(2) Benya, R; Mol Pharmacol 1992, V42(6), P1058 HCAPLUS
(3) Benya, R; Mol Pharmacol 1994, V46(2), P235 HCAPLUS
(5) Erspamer, V; Ann N Y Acad Sci 1988, V547, P3 HCAPLUS
(6) Fathi, Z; J Biol Chem 1993, V268(8), P5979 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 9 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:681001 HCAPLUS
DOCUMENT NUMBER: 130:33276
TITLE: Pharmacology and intracellular signaling mechanisms of the native human orphan receptor BRS-3 in lung cancer cells
AUTHOR(S): Ryan, Richard R.; Weber, H. Christian; Mantey, Samuel A.; Hou, Wei; Hilburger, Mary E.; Pradhan, Tapas K.; Coy, David H.; Jensen, Robert T.
CORPORATE SOURCE: Digestive Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA
SOURCE: J. Pharmacol. Exp. Ther. (1998), 287(1), 366-380
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Neither the native ligand nor the cell biol. of the bombesin (Bn)-related orphan receptor subtype 3 (BRS-3) is known. In this study, the authors used RT-PCR to identify two human lung cancer lines that contain sufficient nos. of native hBRS-3 to allow study: NCl-N417 and NCl-H720. In both cell lines, [DPhe6,.beta.Ala11,Phe13,Nle14]Bn(6-14) stimulates [3H]inositol phosphate. In NCl-N417 cells, binding of 125I-[DTyr6,.beta.Ala11,Phe13,Nle14]Bn(6-14) was saturable and high-affinity. [DPhe6,.beta.Ala11,Phe13,Nle14]Bn(6-14) stimulated phospholipase D activity and a concn.-dependent release of [3H]inositol phosphate (EC50 = 25 nM) and intracellular calcium (EC50 = 14 nM); the increases in intracellular calcium were primarily from intracellular stores. HBRS-3 activation was not coupled to changes in adenylate cyclase activity, [3H]-thymidine incorporation or cell proliferation. No naturally occurring Bn-related peptides bound or activated the hBRS-3 with high affinity. Four different bombesin receptor antagonists inhibited increases in [3H]inositol phosphate. Using cytosensor microphysiometry, the authors found that [DPhe6,.beta.Ala11,Phe13,Nle14]Bn(6-14) caused concn.-dependent acidification. The results show that native hBRS-3 receptors couple to phospholipases C and D but not to adenylate cyclase and that they stimulate mobilization of intracellular calcium and increase metab. but not growth. The discovery of human cell lines with native, functional BRS-3 receptors, of new leads for a more hBRS-3-specific antagonist and of the validity of microphysiometry as an assay has yielded important tools that can be used for the identification of a native ligand for hBRS-3 and for the characterization of BRS-3-mediated biol. responses.
IT **124176-07-4 124199-91-3 130800-28-1 130800-38-3**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(native human orphan receptor BRS-3 pharmacol. and intracellular signaling in lung cancer cells)
REFERENCE COUNT: 42
REFERENCE(S): (1) Akbar, M; FEBS Lett 1994, V348, P192 HCAPLUS
(2) Battey, J; Trends Neurosci 1991, V14, P524 HCAPLUS
(3) Ben-Av, P; Eur J Biochem 1993, V215, P455 HCAPLUS
(4) Benya, R; Mol Pharmacol 1992, V42(6), P1058 HCAPLUS
(5) Benya, R; Mol Pharmacol 1994, V46, P235 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 10 OF 46 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:597605 HCAPLUS
DOCUMENT NUMBER: 129:339929
TITLE: Synthesis and biological evaluation of novel potent bombesin receptor antagonists
AUTHOR(S): Devin, Chantal; Llinares, Muriel; Gagne, Didier; Bernad, Nicole; Azay, Jacqueline; Fehrentz, Jean-Alain; Nagain, Claire; Roze, Claude; Martinez, Jean
CORPORATE SOURCE: Laboratoire des Aminoacides Peptides et Proteines (LAPP) ESA 5075 CNRS, Faculte de Pharmacie, Universites Montpellier I and II, Montpellier, 34060, Fr.
SOURCE: Pept. 1996, Proc. Eur. Pept. Symp., 24th (1998), Meeting Date 1996, 93-96. Editor(s): Ramage, Robert; Epton, Roger. Mayflower Scientific: Kingswinford, UK. CODEN: 66RCA5
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The authors have recently described the synthesis and pharmacol. activities of potent bombesin receptor antagonists in which a pseudopeptide bond replace the peptide bond between the two C-terminal residues in bombesin. The authors report in this paper on one of the most potent for these bombesin receptor antagonists JMV 641, having in its sequence a modified peptide bond between the two last amino acid residues able to mimic the transition state analog of bombesin. The authors also present two new bombesin analogs (JMV 1449, H-dPhe-Gln-Trp-Ala-Val-Gly-His-Leu-NHOH and JMV 1459, H-dPhe-Gln-Trp-Ala-Val-Gly-His-Leu-NHOBzl) without the C-terminal residue but bearing an hydroxamate function, with the hypothesis that this function could interact with an hypothetic metallopeptidase assocd. with the receptor and involved in the mechanism of action of bombesin.
IT **215532-60-8**, JMV 1449 **215532-61-9**, JMV 1459
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(synthesis and biol. evaluation of novel potent bombesin receptor antagonists)

L24 ANSWER 11 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:383062 HCAPLUS
DOCUMENT NUMBER: 129:104499
TITLE: Ability of various bombesin receptor agonists and antagonists to alter intracellular signaling of the human orphan receptor BRS-3
AUTHOR(S): Ryan, Richard R.; Weber, H. Christian; Hou, Wei; Sainz, Eduardo; Mantey, Samuel A.; Battey, James F.; Coy, David H.; Jensen, Robert T.
CORPORATE SOURCE: Digestive Diseases Branch, NIDDK, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE: J. Biol. Chem. (1998), 273(22), 13613-13624 CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Bombesin (Bn) receptor subtype 3 (BRS-3) is an orphan receptor that is a predicted member of the heptahelical G-protein receptor family and so named because it shares a 50% amino acid homol. with receptors for the mammalian bombesin-like peptides neuromedin B (NMB) and gastrin-releasing peptide. In a recent targeted disruption study, in which BRS-3-deficient

mice were generated, the mice developed obesity, diabetes, and hypertension. To date, BRS-3's natural ligand remains unknown, its pharmacol. unclear, and cellular basis of action undetd. Furthermore, there are few tissues or cell lines found that express sufficient levels of BRS-3 protein for study. To define the intracellular signaling properties of BRS-3, the authors examd. the ability of [D-Phe6,.beta.-Ala11,Phe13,Nle14]Bn-(6-14), a newly discovered peptide with high affinity for BRS-3, and various Bn receptor agonists and antagonists to alter cellular function in hBRS-3-transfected BALB 3T3 cells and hBRS-3-transfected NCI-H1299 non-small cell lung cancer cells, which natively express very low levels of hBRS-3. This ligand stimulated a 4-9-fold increase in [3H]inositol phosphate formation in both cell lines under conditions where it caused no stimulation in untransfected cells and also stimulated an increase in [3H]IP1, [3H]IP2, and [3H]IP3. The elevation of [3H]IP was concn.-dependent, with an EC50 of 20-35 nM in both cell lines. [D-Phe6,.beta.-Ala11,Phe13,Nle14]Bn-(6-14) stimulated a 2-3-fold increase in [Ca2+]i, a 3-fold increase in tyrosine phosphorylation of p125FAK with an EC50 of 0.2-0.7 nM, but failed to either stimulate increases in cAMP or inhibit forskolin-stimulated increases. None of nine naturally occurring Bn peptides or three synthetic Bn analogs reported to activate hBRS-3 did so with high affinity. No high affinity Bn receptor antagonist had high affinity for the hBRS-3 receptor, although two low affinity antagonists for gastrin-releasing peptide and NMB receptors, [D-Arg1,D-Trp7,9,Leu11]substance P and [D-Pro4,D-Trp7,9,10]substance P-(4-11), inhibited hBRS-3 receptor activation. The NMB receptor-specific antagonist D-Nal,Cys,Tyr,D-Trp,Lys,Val,Cys,Nal-NH2 inhibited hBRS-3 receptor activation in a competitive fashion (Ki = 0.5 .mu.M). Stimulation of p125FAK tyrosine phosphorylation by hBRS-3 activation was not inhibited by the protein kinase C inhibitor, GF109203X, or thapsigargin, alone or in combination. These results show that hBRS-3 receptor activation increases phospholipase C activity, which causes generation of inositol phosphates and changes in [Ca2+]i and is also coupled to tyrosine kinase activation, but is not coupled to adenylate cyclase activation or inhibition. The hBRS-3 receptor activation results in tyrosine phosphorylation of p125FAK, and it is not dependent on activation of either limb of the phospholipase C cascade. Although the natural ligand is not a known bombesin-related peptide, the availability of [D-Phe6,.beta.-Ala11,Phe13,Nle14]Bn-(6-14), which functions as a high affinity agonist in conjunction with hBRS-3-transfected cell lines and the recognition of three classes of receptor antagonists including one with affinity of 0.5 .mu.M, should provide important tools to assist in the identification of its natural ligand, the development of more potent selective receptor antagonists and agonists, and further exploration of the signaling properties of the hBRS-3 receptor.

IT **124199-91-3 130800-38-3**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(bombesin receptor agonists and antagonists effects on intracellular signaling of the human orphan receptor BRS-3)

L24 ANSWER 12 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:615095 HCAPLUS
DOCUMENT NUMBER: 127:288296
TITLE: Construction of chimeric human bombesin receptors to identify neuromedin B and gastrin-releasing peptide receptor binding sites
AUTHOR(S): Maughfling, Edward J. R.; Boden, Philip; Hall, Matthew D.

CORPORATE SOURCE: Parke-Davis Neuroscience Research Centre, Cambridge University, Cambridge, CB2 2QB, UK
SOURCE: Biochem. Soc. Trans. (1997), 25(3), 455S
CODEN: BCSTB5; ISSN: 0300-5127
PUBLISHER: Portland Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A chimeric receptor strategy was used to detn. which receptor regions are involved in agonist and antagonist binding at human neuromedin B (NMB) and gastrin-releasing peptide (GRP) receptors. Transmembrane region (TM) V was implicated as a major contributor in the binding of NMB at NMB receptors and as important in the binding of neuromedin C at GRP receptors. Thus, residues divergent between GRP receptors and NMB receptors in these regions may confer ligand selectivity. The antagonist PD 16529 appears to act at the same sites. [D-Phe6,des-Met14]bombesin 6-14 ethylamide binds at completely different regions of the receptor (around TM's I, II and VII) suggesting different antagonistic mechanisms.

IT **124199-90-2**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(construction of chimeric human bombesin receptors to identify neuromedin B and gastrin-releasing peptide receptor binding sites)

L24 ANSWER 13 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:586261 HCAPLUS
DOCUMENT NUMBER: 127:257832
TITLE: Bombesin receptor antagonists block the effects of exogenous bombesin but not of nutrients on food intake
AUTHOR(S): Flynn, Francis W.
CORPORATE SOURCE: Department of Psychology and Neuroscience Program, University of Wyoming, Laramie, WY, 82071, USA
SOURCE: Physiol. Behav. (1997), 62(4), 791-798
CODEN: PHBHA4; ISSN: 0031-9384
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The endogenous, meal-contingent release of bombesin (BN)-like peptides is thought to contribute to the termination of a meal. In the following expts. the potency of BN receptor antagonists to attenuate the ability of nutrients to suppress food intake was tested. First, the effectiveness of BN receptor subtype antagonists was verified by testing their ability to block the effects of exogenous BN on food intake. Rats were administered i.p. injections of either saline or 0.1 mg/kg [D-Ph12,Leu14]BN (binds both gastrin-releasing peptide (GRP) and NMB receptors), [D-Phe6]BN(6-13) Et amide (binds GRP > NMB), and cyclo-SS-octa (BIM-23042; binds NMB > GRP). Five minutes later rats were administered 8 .mu.g/kg BN (i.p.) and milk intake was measured. Injections of [D-Phe12,Leu14]BN and [D-Phe6]BN(6-13) Et amide reliably attenuated the ability of BN to suppress milk intake whereas BIM-23042 was ineffective. The results show that the antagonists were behaviorally effective and that exogenous BN may exert its effects of food intake primarily through the GRP receptor subtype. Next, the antagonists were administered either 5 min prior to or 5 min after an intragastric nutrient load or no load in both overnight-deprived and nondeprived rats, and milk intake was then measured. Stomach loads reduced intake and this effect was not attenuated by BN receptor antagonists. Finally, rats were allowed to prefeed and the milk was then removed. Rats were then administered a BN receptor antagonist (0.1 and 1.0 mg/kg) or saline either immediately after the prefeed, 10 min later, or 20 min later. Milk diet was then returned and intake was measured.

Peripheral injections of the BN receptor antagonist had no effect compared to saline on milk intake. Apparently, the blockade of peripheral BN peptide receptors is not sufficient to attenuate the satiety signals generated by stomach loads or prefeeding.

IT **124199-90-2**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(bombesin receptor antagonists block effects of exogenous bombesin but not of nutrients on food intake)

L24 ANSWER 14 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:714931 HCAPLUS
DOCUMENT NUMBER: 126:42790
TITLE: Discovery of high affinity bombesin receptor subtype 3 agonists
AUTHOR(S): Wu, James M.; Nitecki, Danute E.; Biancalana, Sara; Feldman, Richard I.
CORPORATE SOURCE: Department Protein Biochemistry Biophysics, Berlex Biosciences, Richmond, CA, 94804-0099, USA
SOURCE: Mol. Pharmacol. (1996), 50(5), 1355-1363
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Human bombesin receptor subtype 3 (BRS-3) was cloned based on its homol. to the human gastrin-releasing peptide (GRP) receptor and neuromedin B (NMB) receptor. Some bombesin-like peptides were shown to activate BRS-3 expressed in Xenopus laevis oocytes, but only at relatively high concns., which suggests that BRS-3 is an orphan receptor. To study the pharmacol. of BRS-3 in the context of a mammalian cell, we used BR2 cells, which are Balb/3T3 fibroblasts transfected with BRS-3 cDNA. A no. of bombesin-like peptides found in mammals and amphibians stimulated calcium mobilization in BR2 cells but exhibited no effect on nontransfected parental Balb/3T3 cells. Of these peptides, NMB (EC50 .apprx. 1-10 .mu.M) was the most active for stimulation of calcium mobilization. Testing of a series of NMB analogs truncated at the amino terminus and carboxyl terminus indicated that the minimal size of NMB required for retention of full activity was Ac-NMB(3-10). Systematically replacing each residue with alanine, or changing its chirality, demonstrated that the carboxyl-terminal residues His8, Phe9, and Met10 of NMB are important for optimal activity. We also tested whether a no. of bombesin (BN) analogs that are potent pure or partial antagonists of the GRP receptor can activate BRS-3 in BR2 cells. One such analog, D-Phe6-BN(6-13) Pr amide, activated BRS-3-mediated calcium mobilization with an EC50 level of 84 nM. Through addnl. synthesis, we generated a significantly more potent analog, D-Phe6-Phe13-BN(6-13) Pr amide, which displayed an EC50 level of 5 nM for activation of BRS-3. Apparently, the core portions of bombesin-like peptides required for activation of BRS-3 are similar to those necessary for activation of the GRP and NMB receptors and thus provide pharmacol. evidence that BRS-3 is in the BN receptor family. Furthermore, we have identified an agonist of BRS-3, namely D-Phe6-Phe13-BN(6-13) Pr amide, which is roughly 1000-fold more potent than BRS-3 agonists described previously.

IT **124199-90-2 124199-91-3 130800-38-3**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(high-affinity bombesin receptor subtype 3 peptide agonists)

L24 ANSWER 15 OF 46 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1996:439479 HCAPLUS
DOCUMENT NUMBER: 125:105528
TITLE: Pharmacological profiles of two bombesin analogs in cells transfected with human neuromedin B receptors
AUTHOR(S): Ryan, Richard R.; Taylor, John E.; Daniel, James L.; Cowan, Alan
CORPORATE SOURCE: Department of Pharmacology, Temple University School of Medicine, Philadelphia, PA, 19140, USA
SOURCE: Eur. J. Pharmacol. (1996), 306(1-3), 307-314
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors examd. the effect of two des-Met-bombesin analogs, [(CH3)2CHCO-His-Trp-Ala-Val-D-Ala-His-Leu-NHCH3] (ICI 216140) and [D-Phe6,des-Met14]bombesin(6-14) ethylamide (DPDM-bombesin ethylamide), on neuromedin B-induced Ca2+ and [3H]arachidonate release in BALB 3T3 cells transfected with human neuromedin B receptors. ICI 216140 and DPDM-bombesin ethylamide both stimulated Ca2+ mobilization in a concn.-dependent manner but were less potent and efficacious than neuromedin B. BIM 23042 [D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Nal-NH2], a selective neuromedin B antagonist and [D-Arg1,D-Phe5,D-Trp7,9,Leu11]substance P, a broad-spectrum peptide receptor antagonist inhibited neuromedin B-, ICI 216140- and DPDM-bombesin ethylamide-induced Ca2+ release. Pretreatment of cells with either des-Met-bombesin analog attenuated B-induced Ca2+ elevations, suggesting similar agonist-sensitive Ca2+ pools. The pharmacol. profiles revealed from the [3H]arachidonate assay were similar, although ICI 216140 was less potent and efficacious than DPDM-bombesin ethylamide. Apparently, ICI 216140 and DPDM-bombesin ethylamide behave as agonists at the neuromedin B receptor, perhaps as a consequence of neuromedin B receptor overexpression.

IT **124199-90-2**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(pharmacol. profiles of two bombesin analogs in cells transfected with human neuromedin B receptors)

L24 ANSWER 16 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:886494 HCAPLUS
DOCUMENT NUMBER: 123:306760
TITLE: Peptide structural requirements for antagonism differ between the two mammalian bombesin receptor subtypes
AUTHOR(S): Lin, Jaw-Town; Coy, David H.; Mantey, Samuel A.; Jensen, Robert T.
CORPORATE SOURCE: Digestive Diseases Branch (J.-T.L., S.A.M., R. T. J.), Tulane Univ. Medical Center, New Orleans, LA, USA
SOURCE: J. Pharmacol. Exp. Ther. (1995), 275(1), 285-95
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recently it has been established that both a gastrin-releasing peptide (GRP) receptor and a neuromedin B (NMB) receptor mediate the actions of bombesin-related peptides in mammals. Five different classes of peptides that function as GRP receptor antagonists have been identified; however, it is unknown whether similar strategies will yield antagonists for the closely related NMB receptor. In the present study the authors have used either native cells possessing only 1 bombesin (Bn) reactor subtype or cells stably transfected with 1 subtype to det. whether using the strategies that were used successfully for GRP receptors would allow NMB receptor antagonists to be identified. [D-Phe12]Bn analogs; des-Met14

amides, esters and alkylamides; .psi.13-14 Bn pseudopeptides; and D-amino acid-substituted analogs of substance P (SP) or SP(4-11) were all synthesized and each functioned as a GRP receptor antagonist. All of these antagonists had low affinity for the NMB receptor. Application of similar strategies to NMB by formation of [D-Phe8]NMB, [.psi.9-10]NMB pseudopeptides, des-Met10 NMB amides, alkylamide or esters did not result in any potent NMB receptor antagonists. D-Amino acid SP and SP(4-11) analogs were weakly selective NMB receptor antagonists. No C-terminal fragment of NMB or GRP functioned as a GRP or NMB receptor antagonist. These results demonstrate that none of the known strategies used to prep. peptide GRP receptor antagonists are successful at the NMB receptor, such as the formation of somatostatin octapeptide or D-amino acid-substituted substance P analogs. These results suggest that even though there is a close homol. between GRP and NMB and their receptors, their structure-function relations are markedly different. Apparently, the development of receptor subtype-specific peptide agonists or peptide antagonists for newly discovered receptor subtypes of gastrointestinal hormones/neurotransmitters may be difficult because the strategies developed for 1 well-studied subtype may not apply to the other even though it is structurally closely related.

IT **124176-07-4**, [D-Phe6]bombesin(6-13)NH2 **124199-90-2** **124199-91-3** **130800-38-3** **130800-39-4**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(peptide structural requirements for antagonism differ between the two mammalian bombesin receptor subtypes)

L24 ANSWER 17 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:721061 HCAPLUS
DOCUMENT NUMBER: 123:112728
TITLE: Preparation of polypeptide bombesin antagonists.
INVENTOR(S): Schally, Andrew V.; Cai, Ren Zhi
PATENT ASSIGNEE(S): Administrators of the Tulane Educational Fund, USA
SOURCE: PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9421674	A1	19940929	WO 1994-US2511	19940307
W: AU, BR, BY, CA, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, SI, SK, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5369094	A	19941129	US 1993-31325	19930315
AU 9464446	A1	19941011	AU 1994-64446	19940307
AU 666270	B2	19960201		
EP 646127	A1	19950405	EP 1994-912199	19940307
EP 646127	B1	19980701		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 07507330	T2	19950810	JP 1994-521091	19940307
BR 9404341	A	19990831	BR 1994-4341	19940307
PL 180372	B1	20010131	PL 1994-306209	19940307
NO 9404293	A	19950102	NO 1994-4293	19941110
FI 9405378	A	19941115	FI 1994-5378	19941115

PRIORITY APPLN. INFO.:
US 1993-31325 A 19930315
US 1990-619747 A2 19901129
WO 1994-US2511 W 19940307

OTHER SOURCE(S): MARPAT 123:112728

AB X-A1-A2-Trp-Ala-Val-Gly-His-Leu[.PSI.]A9-Q [X = H, bond linking the .alpha.-amino group of A1 to the .gamma.-carboxyl moiety on the 3-propionyl moiety of A2 when A2 is Glu, R1CO; R1 = H, C1-10 alkyl, (substituted) Ph, phenylalkyl, naphthyl, naphthylalkyl, indolyl, indolyalkyl, pyridyl, pyridylalkyl, thienyl, thienylalkyl, cyclohexyl, cyclohexylalkyl, NR2R3, R4O; R2 = H, alkyl, Ph, phenylalkyl; R3 = H, alkyl; R4 = alkyl, Ph, phenylalkyl; A1 = D- or L-pGlu, -Nal, -Pal, -Tpi, (substituted) -Trp, -Phe, peptide bond linking R1CO to the .alpha.-amino moiety of A2; A2 = Gln, Glu[-], Glu(Y), His; [-] = bond linking the .gamma.-carboxyl group of A2 when A2 = Glu with the .alpha.-amino group of A1; Y = OR5, NR5R6; R5 = H, alkyl, phenyl; R6 = H, alkyl; R7 = H, alkyl, NHCONH2; A9 = Tac, MTac, DMTac; Q = NH2, OQ1; Q1 = H, alkyl, Ph, phenylalkyl; Pal = 3-(3-pyridyl)alanyl; Tpi = 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate; Tac = thiazolidine-4-carboxylate; MTac = 2-methylthiazolidine-4-carboxylate; DMTac = 5,5-dimethylthiazolidine-4-carboxylate], were prepd. Thus, H-D-Phe-Gln-Trp-Ala-Val-Gly-His-Leu[.PSI.]Tac-NH2, prepd by solid phase synthesis, inhibited 125I-Tyr4-bombesin binding to swiss 3T3 cells with Ki = 0.078 nM. This compd. at 25 .mu.g/day in mice reduced tumor vol. of estrogen dependent MXT mouse mammary cancer by half after 10 days.

IT **163759-21-5P**

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of polypeptide bombesin antagonists)

L24 ANSWER 18 OF 46 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1995:510685 HCAPLUS

DOCUMENT NUMBER: 122:256743

TITLE: Differential activation of human gastrin-releasing peptide receptor-mediated responses by bombesin analogs

AUTHOR(S): Wu, James M.; Hoang, Danee O.; Feldman, Richard I.

CORPORATE SOURCE: Department of Protein Biochemistry and Biophysics, Berlex Biosciences, Richmond, CA, 94804-0099, USA

SOURCE: Mol. Pharmacol. (1995), 47(4), 871-81
CODEN: MOPMA3; ISSN: 0026-895X

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To enable the detailed pharmacol. characterization of five bombesin (BN) analogs with respect to the human gastrin-releasing peptide (GRP) receptor, the authors ectopically expressed the receptor in BALB/3T3 cells. In such cells (termed GR1 cells), GRP stimulated DNA synthesis and Ca2+ mobilization. Two of these analogs, D-Phe6-BN(6-13) Me ester (Ki = 1.38 nM) and 4-pyridyl-CO-His7-D-Ala11-Lys12-COCH2CH2-phenyl-BN(7-13) Me amide (Ki = 2.17 nM), were pure antagonists of GRP-stimulated DNA synthesis in GR1 cells (IC50 = 14 nM and 5.1 nM, resp.), whereas three analogs, Leu13-.psi.-Leu14-BN (Ki = 21.6 nM), D-Phe6-BN(6-13) Et amide (Ki = 5.17 nM), and D-Phe6-BN(6-13) Pr amide (Ki = 0.68 nM), displayed significant partial agonistic activity. Although three analogs promoted mitogenesis in GR1 cells, none of the analogs stimulated calcium mobilization in GR1 cells. This dichotomy was not limited to transfected cells, because the same result was obtained for D-Phe6-BN(6-13) Pr amide using human fetal lung cells, which naturally express the GRP receptor. The authors also assessed the effect of BN analogs on calcium mobilization in transfected GR9 cells expressing about 30 times higher levels of the GRP receptor, compared with GR1 cells. D-Phe6-BN(6-13) Et amide, D-Phe6-BN(6-13) Pr amide, and Leu13-.psi.-Leu14-BN were partial agonists

of the intracellular Ca2+ mobilization response of GR9 cells. One conclusion consistent with the data is that GRP-stimulated DNA synthesis requires the activation of far fewer receptors than does GRP-stimulated calcium mobilization. Thus, analogs with a small amt. of agonist activity can trigger a mitogenic response but not an intracellular Ca2+ mobilization response, unless cells express a high level of receptors. These studies also provide evidence that the promotion of DNA synthesis is quiescent GR1 or human fetal lung cells via the GRP receptor does not require mobilization of intracellular Ca2+.

IT **124199-90-2 124199-91-3 130800-38-3**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(bombesin analogs in differential activation of human gastrin-releasing peptide receptor-mediated responses)

L24 ANSWER 19 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:396856 HCAPLUS
DOCUMENT NUMBER: 122:178898
TITLE: Fourth ventricular injection of the bombesin receptor antagonist [D-Phe6]bombesin(6-13)methyl ester, but not BW 2258U89, increases food intake in rats
AUTHOR(S): Stratford, Thomas R.; Gibbs, James; Coy, David H.; Smith, Gerard P.
CORPORATE SOURCE: Dep. Psychiatry, White Plains, NY, 10605, USA
SOURCE: Pharmacol., Biochem. Behav. (1995), 50(3), 463-71
CODEN: PBBHAU; ISSN: 0091-3057
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To investigate the role of endogenous bombesin-like peptides in the caudal brainstem for the short-term control of food intake, the authors evaluated the effects of fourth-ventricular injections of 2 different bombesin (BN) receptor antagonists, [D-Phe6]BN(6-13) Me ester and BW 2258U89, on intake of sweetened, condensed milk in male rats. Although fourth-ventricular administration of BW 2258U89 (0.125-20 ng) had no effect on food intake, fourth-ventricular injections of 1.0-20.0 ng of [D-Phe6]Bn(6-13) Me ester and BW 2258U89, on intake of sweetened, condensed milk in male rats. Although fourth-ventricular administration of BW 2258U89 (0.125-20 ng) had no effect on food intake, fourth-ventricular injections of 1.0-20.0 ng of [D-Phe6]BN(6-13) Me ester resulted in an inverted U-shaped, dose-response curve with a maximal effect at 2.5 ng. Microstructural anal. of the licking behavior indicated that the increase in intake was primarily the result of an increased no. of licks and an increase in lick efficiency. Behavioral time sampling demonstrated that these changes in intake occurred without the appearance of any competing behavior or significant change in the overall pattern of behavior. Because [D-Phe6]BN(6-13) Me ester appears to be a preferential antagonist at the GRP-preferring receptor, the increased intake that occurred after its administration suggests that an endogenous GRP-mechanism in the caudal brainstem is necessary for the normal, short-term control of sweet milk intake under these conditions.

IT **130800-38-3**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(fourth ventricular injection of bombesin receptor antagonist increases food intake in rats)

L24 ANSWER 20 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:278612 HCAPLUS
DOCUMENT NUMBER: 123:9930

TITLE: Polypeptide bombesin antagonists
INVENTOR(S): Schally, Andrew V.; Cai, Renzhi
PATENT ASSIGNEE(S): The Administrators of the Tulane Educational Fund, USA
SOURCE: U.S., 36 pp. Cont.-in-part of U.S. 5,244,883.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5369094	A	19941129	US 1993-31325	19930315
US 5244883	A	19930914	US 1990-619747	19901129
CA 2097192	AA	19920530	CA 1991-2097192	19911115
HU 64566	A2	19940128	HU 1993-1567	19911115
HU 213114	B	19970228		
AT 120760	E	19950415	AT 1992-900740	19911115
ES 2072137	T3	19950701	ES 1992-900740	19911115
RU 2115659	C1	19980720	RU 1993-41053	19911115
ZA 9109387	A	19920930	ZA 1991-9387	19911128
CA 2135787	AA	19940929	CA 1994-2135787	19940307
CA 2157871	AA	19940929	CA 1994-2157871	19940307
WO 9421674	A1	19940929	WO 1994-US2511	19940307
W: AU, BR, BY, CA, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, SI, SK, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9464446	A1	19941011	AU 1994-64446	19940307
AU 666270	B2	19960201		
EP 646127	A1	19950405	EP 1994-912199	19940307
EP 646127	B1	19980701		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 07507330	T2	19950810	JP 1994-521091	19940307
HU 69727	A2	19950928	HU 1994-3244	19940307
HU 218288	B	20000728		
RU 2114118	C1	19980627	RU 1994-46091	19940307
AT 167874	E	19980715	AT 1994-912199	19940307
ES 2120615	T3	19981101	ES 1994-912199	19940307
BR 9404341	A	19990831	BR 1994-4341	19940307
CZ 286750	B6	20000614	CZ 1994-2807	19940307
PL 180372	B1	20010131	PL 1994-306209	19940307
ZA 9401767	A	19941006	ZA 1994-1767	19940314
NO 9404293	A	19950102	NO 1994-4293	19941110
FI 9405378	A	19941115	FI 1994-5378	19941115

PRIORITY APPLN. INFO.: US 1990-619747 A2 19901129
US 1993-31325 A 19930315
WO 1994-US2511 W 19940307

OTHER SOURCE(S): MARPAT 123:9930

AB Pseudopeptides comprising a peptide of formula I: X-A1-A2-Trp-Ala-Val-Gly-His-Leu-.psi.-A9-Q wherein X is hydrogen, a single bond linking the .alpha. amino group of A1 to the .gamma. carboxyl moiety on the 3-propionyl moiety of A2 when A2 is Glu, or a group of formula R1CO wherein R1 is selected from the groups consisting of:. (A) hydrogen, C1-10-alkyl, Ph or phenyl-C1-10-alkyl, p-HI-Ph, p-HI-phenyl-C1-10-alkyl, naphthyl, naphthyl-C1-10-alkyl, indolyl, indolyl-C1-10-alkyl, pyridyl, pyridyl-C1-10-alkyl, thienyl, thienyl-C1-10-alkyl, cyclohexyl or cyclohexyl-C1-10-alkyl, where HI = F, Cl, Br, OH, CH3 or OCH3;. (B) N(R2)(R3), wherein R2 is hydrogen, C1-10 alkyl, Ph or phenyl-C1-10-alkyl, R3 is hydrogen or C1-10 alkyl;. (C) R4O, wherein R4 is C1-10 alkyl, Ph or phenyl-C1-10 -alkyl; A1 is a D- or L- amino acid residue selected from the

group consisting of Phe, p-HI-Phe, pGlu, Nal, Pal, Tpi, unsubstituted Trp or Trp substituted in the benzene ring by one or more members selected from the group consisting of F, Cl, Br, NH2 or C1-3 alkyl; or A1 is a peptide bond linking the acyl moiety of R1CO to the .alpha. amino moiety of A2 ; A2 is Gln, Glu[--], Glu(Y) or His, wherein [--] is a single bond linking the .gamma. carboxyl group of A2 when A2 is Glu with the .alpha. amino group of A1 where X is a single bond, Y is OR5 or N(R5)(R6) wherein R5 is hydrogen, C1-3 alkyl or phenyl; R6 is hydrogen or C1-3 alkyl; and R7 is hydrogen, C1-3 alkyl or NHCONH2 ; Leu-.psi. is a reduced form of Leu wherein the C:O moiety is instead CH2 such that the bond of this CH2 moiety with the .alpha. amino group of the adjacent A9 residue is a pseudopeptide bond; A9 is Tac, MTac or DMTac; and Q is NH2 or OQ1 where Q1 is hydrogen, C1-10 alkyl, Ph or phenyl-C1-10 -alkyl; and the pharmaceutically acceptable acids or salts thereof. Inhibition of binding of 125I-Tyr4-bombesin to Swiss 3T3 cells by bombesin antagonists: Ki (nM) from <0.001 to 213. The effects of treatment with bombesin antagonists on tumor vol. of estrogen independent MXT mouse mammary cancers, human small cell lung carcinoma in nude mice, MIA PACA-2 pancreatic cancer tumors, and CAPAN-2 human pancreatic cancer were also reported.

IT **163759-21-5P 163759-31-7P 163759-32-8P**
163759-33-9P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(polypeptide bombesin antagonists as neoplasm inhibitors)

L24 ANSWER 21 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:474504 HCAPLUS
DOCUMENT NUMBER: 121:74504
TITLE: Demethionine-bombesin receptor antagonist blocks bombesin-induced inhibition of alcohol intake
AUTHOR(S): Carr, B. A.; Ballou, J. D.; Marrinan, D. A.; Kulkosky, P. J.
CORPORATE SOURCE: Dep. Psychol., Univ. South Colorado, Pueblo, CO, 81001-4901, USA
SOURCE: Alcohol (N. Y.) (1994), 11(2), 125-31
CODEN: ALCOEX; ISSN: 0741-8329
DOCUMENT TYPE: Journal
LANGUAGE: English

AB [D-Phe6,De-Met14]bombesin(6-14) Et amide (D-BN) is a specific, competitive receptor antagonist of bombesin, a neuropeptide that inhibits alc. and food intake. The effects of i.p. injected D-BN (4-400 .mu.g/kg) were tested on bombesin (4 .mu.g/kg)-induced redn. of caloric intake. In the 1st expt., ad lib-fed female and male rats were deprived of water for 23 h, injected with the peptides or saline in randomized sequences of doses, and immediately given access to 5% EtOH soln. for 30 min, followed by 30 min of water. In a 2nd expt., male rats were injected with the antagonist 10 or 20 min prior to bombesin injection and alc. access, and behaviors were obsd. and quantified once a minute with an instantaneous time-sampling technique. D-BN injection blocked the bombesin-induced redn. of alc. intake (at .gtoreq.40 .mu.g/kg) and food intake (at.gtoreq.200 .mu.g/kg). When injected 20 min prior to access, D-BN alone (200 .mu.g/kg) initially elevated alc. drinking and later increased feeding behaviors and decreased resting, relative to saline injection. The results indicate that bombesin-induced redn. of alc. intake depends on a specific peptidergic receptor process, and endogenous bombesin-like peptides could act physiol. to elicit satiation with EtOH and food.

IT **124199-90-2**
RL: BIOL (Biological study)

(ethanol consumption inhibition by bombesin blockade by)

L24 ANSWER 22 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:404222 HCAPLUS
DOCUMENT NUMBER: 121:4222
TITLE: Tools for investigating functional interactions between ligands and G-protein-coupled receptors
AUTHOR(S): Lerner, Michael R.
CORPORATE SOURCE: Sch. Med., Yale Univ., New Haven, CT, 06536-0812, USA
SOURCE: Trends Neurosci. (1994), 17(4), 142-6
CODEN: TNSCDR; ISSN: 0166-2236
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A general assay for evaluating functional interactions between ligands and G-protein-coupled receptors within minutes has been developed. The system uses the principles employed by animals such as reptiles, amphibians and fish to control their colors. In nature, activation of G-protein-coupled receptors expressed by skin cells called chromatophores effects pigment redistribution within the cells to change an animal's coloration. The in vitro chameleon in a dish equiv. can use essentially any cloned G-protein-coupled receptor.
IT **130800-38-3**
RL: ANST (Analytical study)
(frog melanophores expressing recombinant G-protein-coupled murine bombesin receptor response to)

L24 ANSWER 23 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:96458 HCAPLUS
DOCUMENT NUMBER: 120:96458
TITLE: Two bombesin analogs discriminate between neuromedin B- and bombesin-induced calcium flux in a lung cancer cell line
AUTHOR(S): Ryan, R. R.; Daniel, J. L.; Cowan, A.
CORPORATE SOURCE: Sch. Med., Temple Univ., Philadelphia, PA, 19140, USA
SOURCE: Peptides (Pergamon) (1993), 14(6), 1231-5
CODEN: PPTDD5; ISSN: 0196-9781
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors examd. the profile of two bombesin (BN) antagonists, (CH3)2CHCO-His-Trp-Ala-Val-D-Ala-His-Leu-NHCH3 (ICI 216140) and [D-Phe6,des-Met14]BN(6-14)ethylamide (DPDM-BN EA), against neuromedin B-induced Ca2+ mobilization in the small cell lung cancer (SCLC) line NCI-H345. Neuromedin B (NMB), a BN-like peptide sharing sequence homol. with ranatensin, elicited a concn.-dependent Ca2+ release (in part) from intracellular stores. Sequential addn. of NMB attenuated Ca2+ mobilization. Desensitization occurred between BN and NMB; depletion of intracellular Ca2+ is a likely mechanism because thapsigargin stimulated Ca2+ release after a maximally desensitizing dose of NMB. ICI 216140 and DPDM-BN EA competitively inhibited BN-induced Ca2+ transients. In contrast, these compds. antagonized NMB-stimulated Ca2+ transients in a noncompetitive manner. The pharmacol. profiles obtained support receptor heterogeneity for BN-like peptides on this SCLC line, underscoring the need for thorough examn. of dose-response relationships when investigating effects of BN analogs on intact cells.
IT **124199-90-2**
RL: BIOL (Biological study)
(calcium transport inhibition by, in lung neoplasm after bombesin and neuromedin B stimulation)

L24 ANSWER 24 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:23724 HCAPLUS
DOCUMENT NUMBER: 120:23724
TITLE: Structure-activity requirements of bombesin for gastrin-releasing peptide- and neuromedin B-preferring bombesin receptors in rat brain
AUTHOR(S): Guard, Steven; Watling, Keith J.; Howson, William
CORPORATE SOURCE: Parke-Davis Neurosci. Res. Cent., Addenbrookes Hosp., Cambridge, CB2 2QB, UK
SOURCE: Eur. J. Pharmacol. (1993), 240(2-3), 177-84
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The pharmacol. profile of [125I][Tyr4]bombesin binding to gastrin-releasing peptide- and neuromedin B-preferring sites has been investigated in rat cerebral cortex and olfactory bulk membranes, resp. [125I][Tyr4]bombesin specific binding to cerebral cortex membranes was displaced biphasically by gastrin releasing peptide and [D-Phe6]bombesin-(6-13)-Et amide. In the presence of 10 nM neuromedin B, displacement curves for bombesin-related peptides were monophasic with gastrin releasing peptide displaying approx. 100-fold higher affinity than neuromedin B. In olfactory bulb membranes, [125I][Tyr4]bombesin binding was also displaced biphasically by gastrin releasing peptide, [D-Phe6]bombesin-(6-13)-Et amide and neuromedin B. In the presence of 10 .mu.M [D-Phe6]bombesin-(6-13)-Et ester, displacement curves were monophasic with neuromedin B possessing approx. 10-fold higher affinity than gastrin-releasing peptide. Under these conditions, successive deletion of N-terminal amino acids from bombesin-(1-14) was well tolerated at both sites, with little loss in affinity up to bombesin-(5-14). A 5- to 10-fold drop in affinity was obsd. at both sites with bombesin-(6-14), while the octapeptide acetyl-bombesin-(7-14) displayed similar affinities to bombesin-(1-14). Bombesin-(8-14), -(9-14) and -(10-14) were essentially inactive (IC50 > 10 .mu.M). C-terminal deletion of Met14 (bombesin-(1-13)) resulted in 100-fold loss of affinity at the gastrin-releasing peptide site and complete loss of affinity at the neuromedin B site. Fragments smaller than bombesin-(1-13) were virtually inactive at either site. Replacement of consecutive amino acids in the minimal active fragment, acetyl-bombesin-(7-14), with L-alanine revealed the crit. importance of Trp8 and Leu13 for binding to both sites.
IT **124199-90-2 130800-39-4**
RL: BIOL (Biological study)
(gastrin-releasing peptide- and neuromedin B-preferring bombesin receptors affinity for, of brain, structure in relation to)

L24 ANSWER 25 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:641685 HCAPLUS
DOCUMENT NUMBER: 119:241685
TITLE: A potent bombesin receptor antagonist inhibits bombesin-stimulated growth of mouse colon cancer cells in vitro: Absence of autocrine effects
AUTHOR(S): Narayan, Satya; Spindel, Eliot R.; Rubin, Norma H.; Singh, Pomila
CORPORATE SOURCE: Dep. Surg., Univ. Texas M, Galveston, TX, 77550, USA
SOURCE: Cell Growth Differ. (1992), 3(2), 111-18
CODEN: CGDIE7; ISSN: 1044-9523
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Bombesin (BBS) exerts significant effects on the growth of a mouse colon cancer cell line (MC-26) in vitro. The presence of specific binding sites

on MC-26 cells for gastrin-releasing peptide (GRP)/BBS-related peptides was recently reported by the authors. In the present study, the authors detd. that the transcript size of the mRNA species that codes for GRP receptors is 9 kilobase pairs, which is similar to that reported for mouse Swiss 3T3 cells, using the complementary DNA probe for the GRP receptor gene from mouse Swiss 3T3 cells. The authors next examd. the effects of potent GRP receptor antagonists, D-Phe6, bombesin(6-13)-propylamide (D-Phe6,BN(6-13)PA) and Leu13-.psi.-(CH2NH)Leu14-bombesin (LL-BBS), on BBS-stimulated growth of MC-26 cells in vitro. A possible autocrine role of GRP in the growth of MC-26 cells was also investigated. MC-26 cells were inoculated s.c. into male BALB/c mice, and tumors were harvested 21-28 days postinoculation. Both D-Phe6,BN(6-13)PA and LL-BBS inhibited the binding of 125I-GRP to MC-26 tumor membranes in a dose-dependent manner, with 50% inhibitory concns. of 4.5 nM and 87 nM, resp. D-Phe6,BN(6-13)PA similarly inhibited the specific binding of 125I-GRP, cross-linked to a .apprx.80 kDa binding protein on the MC-26 tumor membranes. To det. whether the BBS receptor antagonist, D-Phe6,BN(6-13)PA, functioned as an antagonist or an agonist of biol. functions, the authors measured the bioefficacy of D-Phe6,BN(6-13)PA. Amylase release was not stimulated at all doses of D-Phe6,BN(6-13)PA examd., but the release of amylase in response to BBS was inhibited in a dose-dependent manner by D-Phe6,BN(6-13)PA with a 50% inhibitory concn. of 2.90 nM. The growth of MC-26 cells in response to a maximally ED of BBS (50 nM) was inhibited in the presence of increasing doses of D-Phe6,BN(6-13)PA and LL-BBS; D-Phe6,BN(6-13)PA and LL-BBS had no significant effects on the growth of MC-26 cells in the absence of BBS. Because the antagonists did not alter the growth of MC-26 cells in the absence of BBS, the authors hypothesized that MC-26 cells were not releasing BBS-like peptides into the medium; this possibility was confirmed by the authors' inability to measure GRP gene expression by Northern hybridization of total and polyadenylated RNA with labeled complementary DNA probe for rat GRP gene. The authors' studies thus indicate that, unlike small cell lung cancers, BBS is not an autocrine growth factor for mouse colon cancers.

IT **124199-91-3**
RL: BIOL (Biological study)
(colon neoplasm growth-inhibiting activity of , after bombesin stimulation)

L24 ANSWER 26 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:509435 HCAPLUS
DOCUMENT NUMBER: 119:109435
TITLE: Solubilization and purification of bombesin/Gastrin releasing peptide receptors from human cell lines
AUTHOR(S): Staley, Julie; Coy, D. H.; Jensen, R. T.; Moody, Terry W.
CORPORATE SOURCE: Med. Cent., George Washington Univ., Washington, DC, 20037, USA
SOURCE: J. Mol. Neurosci. (1993), 4(1), 29-40
CODEN: JMNEES; ISSN: 0895-8696
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Bombesin/gastrin releasing peptide (BN/GRP) receptors were solubilized and purified from human glioblastoma (U-118) and lung carcinoid cell lines (NCI-H720). The U-118 cells, when extd. with CHAPS/cholesterol hemisuccinate (CHS), bound (125I-Tyr4)BN with high affinity (Kd = 2 nM) to a single class of sites (Bmax = 150 fmol/mg protein). Specific (125I-Tyr4)BN binding was inhibited with high affinity by BN, GRP, GRP14-27, and receptor antagonists such as (D-Phe6)BN6-13 Me ester(ME) and

(D-Phe6)BN6-13 propylamide(PA) (IC50 = 2, 22, 3, 1 and 2 nM, resp.) but not GRP1-16 or BN1-12. The solubilized and cellular receptor bound peptides with similar affinity. The solubilized receptor was purified using (Lys0,Gly1-4,D-Ala5)BN and (Lys3,Gly4,5,D-Tyr6)BN3-13 PA affinity resins. When eluted from the affinity resins by NaCl, the receptor bound (125I-D-Tyr6)BN6-13 ME with high affinity. The NCl-H720 BN/GRP receptor was purified 86,000-fold after extn. with CHAPS/CHS and purifn. using both affinity resins. SDS-PAGE anal. indicated that major 65 and 115 kDa proteins were purified. These data indicate that BN/GRP receptors can be solubilized from human cells and purified using affinity chromatog. techniques with retention of ligand binding activity.

IT **124199-91-3P 130800-38-3P**
RL: PREP (Preparation)
(bombesin/gastrin releasing peptide receptors binding of, after solubilization and purifn. from human cells)

L24 ANSWER 27 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:486775 HCAPLUS
DOCUMENT NUMBER: 119:86775
TITLE: Bombesin receptor antagonists differentiate receptor subtypes in rat brain
AUTHOR(S): Ladenheim, Ellen E.; Jensen, Robert T.; Mantey, Samuel A.; Taylor, John E.; Coy, David H.; Moran, Timothy H.
CORPORATE SOURCE: Sch. Med., Johns Hopkins Univ., Baltimore, MD, 21205, USA
SOURCE: Eur. J. Pharmacol. (1993), 235(1), 121-5
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Previous studies have shown that various bombesin receptor antagonists can distinguish between bombesin receptor subtypes in peripheral tissues. To det. whether these antagonists would be useful in differentiating bombesin receptor subtypes in the rat central nervous system, in vitro receptor autoradiog. was used to examine the binding affinities of the bombesin receptor antagonists [D-Phe6]bombesin-(6-13) Et ester, [D-F5,Phe6,D-Ala11]bombesin-(6-13) Me ester, and [D-Phe6,Cpa14,.psi.13-14]bombesin-(6-14) and the partial agonist [D-Phe6]bombesin-(6-13) butylamide for gastrin-releasing peptide binding sites in the suprachiasmatic or supraoptic nucleus or for [D-Tyr0]neuromedin B binding sites in the anterior olfactory nucleus. Consistent with peripheral bombesin receptors, bombesin receptor subtypes in the rat brain can be differentiated by various bombesin receptor antagonists.

IT **130800-27-0 130800-39-4**
RL: BIOL (Biological study)
(gastrin-releasing peptide and neuromedin B binding sites of brain differentiation by)

L24 ANSWER 28 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:205226 HCAPLUS
DOCUMENT NUMBER: 118:205226
TITLE: Bombesin analogs for treatment of liver cancer
INVENTOR(S): Bodgen, Arthur E.; Coy, David H.; Kim, Sun Hyuk; Moreau, Jacques Pierre
PATENT ASSIGNEE(S): Biomeasure, Inc., USA; Tulane Educational Fund
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9220363	A1	19921126	WO 1992-US3916	19920511
W: CA, HU, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				
US 6083915	A	20000704	US 1991-698681	19910510
EP 588873	A1	19940330	EP 1992-911903	19920511
EP 588873	B1	19970312		
R: DE, FR, GB, IT				
JP 06507633	T2	19940901	JP 1992-511169	19920511
AT 149840	E	19970315	AT 1992-911903	19920511
ES 2101100	T3	19970701	ES 1992-911903	19920511

PRIORITY APPLN. INFO.: US 1991-698681 A 19910510
WO 1992-US3916 W 19920511

AB Bombesin analogs (Markush included) are disclosed for treatment of liver cancer. Prepn. of selected bombesin analogs is described. Thus, D-p-ChloroPhe-Gln-Trp-Ala-Val-Gly-His-Leu-.psi.[CH2NH]-Phe-NH2 (BIM-26159) inhibited the growth of hepatoma cells implanted in athymic female mice; at all 3 doses tested, there was a significant redn. (approx. 20%) in the growth of the liver tumor over a 13 day period.

IT **124176-07-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, for hepatoma inhibitor)

L24 ANSWER 29 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:16904 HCAPLUS
DOCUMENT NUMBER: 118:16904
TITLE: Neuromedin B binds with high affinity, elevates cytosolic calcium and stimulates the growth of small-cell lung cancer cell lines
AUTHOR(S): Moody, Terry W.; Staley, Julie; Zia, Farah; Coy, David H.; Jensen, Robert T.
CORPORATE SOURCE: Sch. Med. Health Sci., George Washington Univ., Washington, DC, USA
SOURCE: J. Pharmacol. Exp. Ther. (1992), 263(1), 311-17
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Previously, gastrin-releasing peptide (GRP) receptors were identified on small-cell lung cancer (SCLC) cells and GRP functioned as a SCLC autocrine growth factor. Here the effects of neuromedin B (NMB) on SCLC cells were investigated. [125I-Tyr0]NMB bound with high affinity to 3 of 7 SCLC cell lines examd. [125I-Tyr0]NMB bound to SCLC cell line NCl-H209 and NCl-H345 in a time-dependent and reversible manner. [125I-Tyr0]NMB bound with high affinity (Kd = 1 nM) to a single class of sites (Bmax = 800/cell). Specific [125I-Tyr0]NMB binding was inhibited with high affinity by NMB (IC50 = 1 nM) and moderate affinity by bombesin, GRP and [D-Arg1,D-Pro2,D-Trp7,9,Leu11]substance P ([APTTL]SP) but not GRP1-16 (IC50 = 50, 100, 1000 and > 10,000 nM, resp.). In Fura 2 AM loaded NCl-H345 cells, NMB elevated cytosolic Ca in a concn.-dependent manner. NMB (10 nM) elevated the cytosolic Ca from 150 to 180 nM and Ca was released from intracellular pools. The increase in cytosolic Ca caused by 10 nM NMB was reversed by 1 .mu.M [APTTL]SP but not 1 .mu.M [D-Phe6]bombesin6-13 Me ester, a GRP receptor antagonist. Also, NMB stimulated the clonal growth of NCl-H209 and NCl-H345 in a concn.-dependent manner. The increase in the clonal growth caused by NMB was reversed by 1 .mu.M [APTTL]SP. These data suggest that NMB receptors

may regulate the proliferation of some SCLC cells.
IT **130800-38-3**
RL: BIOL (Biological study)
(bombesin receptors binding by, in small cell lung carcinoma)

L24 ANSWER 30 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:625864 HCAPLUS
DOCUMENT NUMBER: 117:225864
TITLE: Antitumoral activity of bombesin analogs on small cell lung cancer xenografts: relationship with bombesin receptor expression
AUTHOR(S): Thomas, Francois; Arvelo, Francisco; Antoine, Etienne; Jacrot, Michelle; Poupon, Marie France
CORPORATE SOURCE: Ipsen Biotech., Paris, 75737, Fr.
SOURCE: Cancer Res. (1992), 52(18), 4872-7
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Gastrin releasing peptide (GRP), the human homolog of bombesin (BN), is an autocrine growth factor for small cell lung cancer (SCLC) cells. The synthetic octapeptides [D-cpa1-.beta.-Leu8-des-met9]litorin (BIM 26182) and [D-Phe6-Leu13-CH2NH-Cpa14]bombesin(6-14)NH2 (BIM 26189) are potent GRP/BN antagonists of the proliferation of 3T3 and rat pancreas cells. The effect of these analogs on the proliferation of four SCLC cell lines (SCLC 6, SCLC 41, SCLC 75, SCLC 74R) was tested in vitro and in vivo. Two of these SCLC lines (SCLC 41M and SCLC 75) had receptors for BN/GRP and expressed the prepro-GRP mRNA. BIM 26182 and BIM 26189 inhibited [3H]thymidine incorporation into the DNA of SCLC 41 cells, stimulated by [3H]thymidine incorporation in SCLC 6, and had no effect on the two other cell lines. The SCLC implanted s.c. in nude mice were treated with either BIM 26182 or BIM 26189. BIM 26182 and BIM 26189 injected at the doses of 50 .mu.g twice a day (s.c.) around the tumor for 10 to 21 days delayed the growth of SCLC 41 and of SCLC 75. The maximal effect was obsd. during the treatment period, after which the tumors regrew, suggesting a cytostatic effect of these peptides. No inhibitory effect of the peptides on SCLC 74R or SCLC 6 growth was obsd. These data suggest that GRP antagonists are able to inhibit the in vitro and in vivo growth of BN/GRP receptor-pos. SCLC.
IT **124199-86-6**, BIM 26182
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor activity of, in small cell lung cancer, gastrin releasing peptide receptor antagonism in)

L24 ANSWER 31 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:605545 HCAPLUS
DOCUMENT NUMBER: 117:205545
TITLE: Development of a potent bombesin receptor antagonist with prolonged in vivo inhibitory activity on bombesin-stimulated amylase and protein release in the rat
AUTHOR(S): Coy, D. H.; Mungan, Z.; Rossowski, W. J.; Cheng, B. L.; Lin, J. T.; Mrozinski, J. E., Jr.; Jensen, R. T.
CORPORATE SOURCE: Med. Cent., Tulane Univ., New Orleans, LA, 70112, USA
SOURCE: Peptides (Pergamon) (1992), 13(4), 775-81
CODEN: PPTDD5; ISSN: 0196-9781
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Of the various types of potent bombesin(Bn)/gastrin releasing peptide

receptor antagonists that have been discovered, the desMet14-Me ester peptides are devoid of residual agonist activity and are among the most potent in terms of in vitro receptor blockade and also in terms of their prolonged inhibition of bombesin-stimulated amylase and protein release in the rat. Thus, the in vitro and in vivo properties of a new series of Me ester analogs, [D-Phe6]Bn(6-13)OMe, [D-Phe6,D-Ala11]Bn(6-13)OMe, N.alpha.-propionyl-[D-Ala24]GRP(20-26)OMe, and [D-pentafluoro-Phe6,D-Ala11]Bn(6-13)OMe, which have an addnl. D-amino acid substituent and some highly lipophilic moieties at the N-terminus were examd.. All analogs were able to potently antagonize the ability of Bn to stimulate amylase release from rat acinar cells comparable to Bn itself, with Kis of 10.3, 2.8, 5.5, and 3.6 nM, resp., but all had little or no affinity for neuromedin B receptors on murine C6 cells. Single bolus i.v. injections of these peptides potently inhibited amylase and protein release caused by i.v. infusion of bombesin into the rat.

IT **130800-38-3**
RL: BIOL (Biological study)
(as bombesin receptor antagonist, pancreas amylase and protein release inhibition by)

L24 ANSWER 32 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:564325 HCAPLUS
DOCUMENT NUMBER: 117:164325
TITLE: Activation of neuromedin B-preferring bombesin receptors on rat glioblastoma C-6 cells increases cellular calcium and phosphoinositides
AUTHOR(S): Wang, Lu Hua; Battey, James F.; Wada, Etsuko; Lin, Jaw Town; Mantey, Samuel; Coy, David H.; Jensen, Robert T.
CORPORATE SOURCE: Dig. Dis. Branch, Natl. Inst. Health, Bethesda, MD, 20892, USA
SOURCE: Biochem. J. (1992), 286(2), 641-8
CODEN: BIJOAK; ISSN: 0306-3275
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recent cloning studies confirm the presence of two subtypes of bombesin (Bn) receptors. In contrast to the gastrin-releasing peptide (GRP)-preferring subtype, which has been widely studied, nothing is known about the cellular mechanisms of the neuromedin B (NMB)-preferring subtype, which occurs widely in the central nervous system and gastrointestinal tissues, partially because of the lack of a cell line with functional receptors. In the present study Bn receptors were investigated on the rat glioblastoma cell line C-6, reported to contain mRNA of the NMB receptor subtype. Binding of 125I-[D-Tyr0]NMB to these cells was time- and temp.-dependent, saturable, reversible, and only inhibited by Bn receptor agonists or antagonists. For Bn receptor agonists the relative potencies were: NMB (1.7 nM) .simeq. litorin (2 nM) > ranatensin (8 nM) > Bn (19 nM) > neuromedin C (NMC) (210 nM) > GRP (500 nM). These relative affinities were almost identical to those for the NMB receptor subtype on rat esophageal tissue and for Balb 3T3 cells stably transfected with this receptor, and differed markedly from those for binding to the GRP receptor subtype on rat pancreatic acini. Four Bn receptor antagonists had a higher affinity for the GRP subtype {[D-Phe6]Bn-(6-13)ethyl ester (500-fold); [D-Phe6][.psi.13-14,Leu13,Cpa14]Bn-(6-14) (where .psi.13-14 refers to the replacement of the -CONH- peptide bond between Leu13 and Met14 by -CH2NH2) (70-fold); [.psi.13-14, Leu14]Bn (50-fold); and [D-Phe6]Bn-(6-13)propylamide (30-fold)}. Two had a higher affinity for the NMB subtype on C-6 cells and transfected cells {[D-Pro4,D-Trp7,9,10]substance P-(4-11) (9-fold) and [Tyr4,D-Phe12]Bn (18-fold)}. In C-6 tumor cells, Bn receptor agonists

caused an increase in cytosolic Ca2+ and the generation of inositol phosphates. For both responses, NMB was more than 50-fold more potent than GRP. Neither NMB nor GRP increased cAMP. These results demonstrate that the rat glioblastoma cell line C-6 processes functional NMB-preferring Bn receptors, and agonist occupation activates phospholipase C, thus increasing cytosolic Ca2+ and inositol phosphate formation. Because the interaction of Bn-related peptides with C-6 cell receptors is identical with that reported in other tissues contg. the mRNA for the NMB subtype, this cell line should prove useful in exploring further the cellular basis of action of the peptides that interact with this receptor in the central nervous system and various other tissues.

IT **124199-91-3 130800-39-4**
RL: BIOL (Biological study)
(bombesin binding to pancreatic gastrin-releasing peptide receptor and neuromedin binding by glioblastoma bombesin receptor inhibition by)

L24 ANSWER 33 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:564313 HCAPLUS
DOCUMENT NUMBER: 117:164313
TITLE: Effect of [D-Phe6] bombesin (6-13) methylester, a bombesin receptor antagonist, towards bombesin-induced contractions in the guinea pig and rat isolated urinary bladder
AUTHOR(S): Maggi, Carlo Alberto; Coy, David H.; Giuliani, Sandro
CORPORATE SOURCE: Pharmacol. Dep., A. Menarini Pharm., Florence, 50131, Italy
SOURCE: J. Auton. Pharmacol. (1992), 12(4), 215-22
CODEN: JAPHDU; ISSN: 0144-1795
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of [D-Phe6]bombesin (6-13) methylester (OMe), a newly developed potent antagonist of bombesin receptors, has been investigated against bombesin-induced contractions of the guinea pig and rat isolated urinary bladder. Bombesin (0.1 nM-10 .mu.M) produced a concn.-dependent contraction of the guinea pig isolated bladder which approached the same max. response as KCl (80 mM). The response to bombesin was antagonized in a competitive manner (rightward shift of the concn.-response curve without depression of the maximal response) by [D-Phe6]bombesin(6-13) OMe (0.3-10 .mu.M). Degree of antagonism was concn.-dependent between 0.3 and 3 .mu.M (dose ratios = 2.4, 9, and 39 in the presence of 0.3, 1, 3 .mu.M of the antagonist). However, a larger concn. (10 .mu.M) of the antagonist was not more effective (dose ratio = 36) than 3 .mu.M. Neither the action of bombesin nor the activity of the antagonist was influenced by peptidase inhibitors (bestatin, captopril, and thiorphan 3 .mu.M each) or by atropine, indomethacin, chlorpheniramine and desensitization of P2x purinoceptors by .alpha.,.beta.-methylene ATP. The bombesin antagonist was ineffective against contraction of the guinea pig urinary bladder produced by the NK-1 tachykinin receptor-selective agonist, [Sar9]substance P sulfone. The action of the NK-1 receptor agonist was antagonized by L 668,169 (3 .mu.M), a cyclic peptide tachykinin antagonist. L 668,169 had no effect toward bombesin-induced contraction. The bombesin antagonist (1-10 .mu.M) had no effect against the nonadrenergic noncholinergic response of the guinea pig isolated urinary bladder to elec. field stimulation. Likewise, the bombesin antagonist (10 .mu.M) did not affect the contraction produced by capsaicin (10 .mu.M) on muscle strips from the dome of the guinea pig urinary bladder. Bombesin (1 nM-1 .mu.M) produced concn.-dependent contraction of the rat isolated bladder which was unaffected by [D-Phe6]bombesin(6-13) OMe (10 .mu.M), which alone produced a contraction of the isolated rat bladder, suggesting

partial agonist activity. Apparently, [D-Phe6]bombesin (6-13) OMe is a suitable antagonist for establishing the putative role of bombesin in the guinea pig urinary bladder, although the nature of its action at this level cannot be explained by simple competition of 1 bombesin receptor only. The failure of [D-Phe6]bombesin(6-13) OMe to antagonize the action of bombesin in the rat urinary bladder suggests that different mechanisms (receptors) mediate the response to this peptide in the urinary bladder of different species. These findings fail to reveal any role for a bombesin-like peptide as excitatory transmitter in the guinea pig urinary bladder nor indicate a role for bombesin-like peptides as mediators of the efferent function of capsaicin-sensitive primary afferents.

IT **130800-38-3**
RL: BIOL (Biological study)
(bombesin antagonism by, in urinary bladder contraction, species in relation to)

L24 ANSWER 34 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:483809 HCAPLUS
DOCUMENT NUMBER: 117:83809
TITLE: Metabolic stability and tumor inhibition of bombesin/GRP receptor antagonists
AUTHOR(S): Davis, T. P.; Crowell, S.; Taylor, J.; Clark, D. L.; Coy, D.; Staley, J.; Moody, T. W.
CORPORATE SOURCE: Coll. Med., Univ. Arizona, Tucson, AZ, 85724, USA
SOURCE: Peptides (Pergamon) (1992), 13(2), 401-7
CODEN: PPTDD5; ISSN: 0196-9781
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Small cell lung cancers (SCLC) synthesize and secrete bombesin/gastrin releasing peptide (BN/GRP). The autocrine growth cycle of BN/GRP in SCLC can be disrupted by BN/GRP receptor antagonists such as [Psi13,14]BN. Several BN analogs were solid-phase synthesized and incubated with intact SCLC cells at 37.degree. in RPMI medium in a time-course fashion (0-1080 min) to det. enzymic stability. The proteolytic stability of the compds. was detd. by subsequent HPLC anal. The metabolic half-life ranged from 154 min to 1388 min for the six analogs studied. [Psi13,14]BN was very stable to metabolic enzymes (T1/2 = 646 min) and also inhibited SCLC xenograft formation in vivo in a dose-dependent manner. When [Psi13,14]BN was incubated with NCI-H345 cells, it inhibited 125I-GRP binding with an IC50 value of 30 nM. Thus, BN/GRP receptor antagonists such as [Psi13,14]BN may be useful for the treatment of SCLC.

IT **142828-01-1**
RL: BIOL (Biological study)
(antitumor and bombesin receptor antagonist activity and stability of, in small cell lung cancer)

L24 ANSWER 35 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:129652 HCAPLUS
DOCUMENT NUMBER: 116:129652
TITLE: Preparation of (cyclic) peptides as neoplasm inhibitors
INVENTOR(S): Coy, David H.; Kim, Sun Hyuk; Moreau, Jacques Pierre
PATENT ASSIGNEE(S): Tulane Educational Fund, Inc., USA; Biomeasure, Inc.
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9117181	A1	19911114	WO 1991-US3265	19910509
W: BG, CA, FI, HU, JP, NO, PL, RO, SU				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
EP 531342	A1	19930317	EP 1991-909510	19910509
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
HU 62904	A2	19930528	HU 1992-3481	19910509
JP 05506862	T2	19931007	JP 1991-509428	19910509
NO 9204293	A	19930106	NO 1992-4293	19921106
PRIORITY APPLN. INFO.:			US 1990-520226	19900509
			WO 1991-US3265	19910509

OTHER SOURCE(S): MARPAT 116:129652

AB Peptides R1R2A-A1-A1-A2-A3-A4-A5-A6-A7-A8-A9-R3 [A = Gly, D-or L-isomer of Nle, Ala, Val, etc.; A1 = D- or L-isomer of Nle, Ala, Val, Gln, etc.; A2 = Gly, D- or L-isomer of Ala, Val, Gln, Asn, etc.; A3 = D- or L-isomer of p-X-Phe (X = H, halo, etc.), .beta.-naphthylalaninyl residue, Trp; A4 = Ala, Val, Gln, Asn, Gly, etc.; A5 = Gln, Asn, Gly, Ala, Leu, etc.; A6 = Sar, Gly, D-Ala, D-Val, etc.; A7 = MeHis, His, Lys, Asp, Glu; A8 = Leu, Ile, Val, Nle, Thr, etc.; A9 = Met, Met(SO), Leu, Ile, etc.; R1, R2 = H, C1-12 alkyl, C7-10 phenylalkyl, COR, C1-12 acyl; R = C1-20 alkyl, C3-20 alkenyl, Ph, naphthyl, C3-20 alkynyl; R3 = H, NH2, C1-12 alkyl, C7-10 phenylalkyl, C3-20 naphthylalkyl; with provisos] and cyclic analogs were prepd. as analogs of litorin, amphibian bombesin, 10 amino acid C-terminal ends of mammalian GRP, neuromedin B, or neuromedin C. They are agonists of the naturally occurring peptides useful as, for example, neoplasm inhibitors (no data). Thus, bombesin agonist D-Phe-Gln-Trp-Ala-Val-Gly-His-Leu-Leu-NH2 was prepd. with 4-methylbenzhydrylamine-polystyrene resin (Cl- form) and the appropriate BOC-protected amino acids. The peptide was cleaved by anisole and dithioerythritol in HF.

IT **124199-91-3P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of, as neoplasm inhibitor)

L24 ANSWER 36 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:716 HCAPLUS
DOCUMENT NUMBER: 116:716
TITLE: Peptide analogs of bombesin and others for treatment of cancer
INVENTOR(S): Bogden, Arthur E.; Moreau, Jacques Pierre
PATENT ASSIGNEE(S): Biomeasure, Inc., USA
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9104040	A1	19910404	WO 1990-US5271	19900917
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
US 5217955	A	19930608	US 1990-520225	19900505
CA 2042027	AA	19910316	CA 1990-2042027	19900917
EP 448677	A1	19911002	EP 1990-915233	19900917
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE				

JP 04503075	T2	19920604	JP 1990-514039	19900917
US 5736517	A	19980407	US 1993-73771	19930608

PRIORITY APPLN. INFO.:
US 1989-408125 19890915
US 1989-440039 19891121
US 1990-520225 19900505
WO 1990-US5271 19900917

OTHER SOURCE(S): MARPAT 116:716

AB Nonmalignant proliferative disease and cancer in human patients are treated by administration of an inhibiting amt. of a peptide analog of mammalian gastrin-releasing peptide, neuromedin B, neuromedin C, amphibian bombesin, or litorin. Bombesin analog peptides were synthesized by solid-phase synthesis using benzhydrylamine-polystyrene resins and tested for antitumor activity against rat and human tumor lines.

IT **124199-90-2 124199-91-3**
RL: BIOL (Biological study)
(cancer and proliferative disease treatment with)

IT **124176-07-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as litorin analog)

L24 ANSWER 37 OF 46 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1991:648262 HCAPLUS
DOCUMENT NUMBER: 115:248262
TITLE: Comparison of prolonged in vivo inhibitory activity of several potent bombesin (BN) antagonists on BN-stimulated amylase secretion in the rat
AUTHOR(S): Alptekin, N.; Yagci, R. V.; Ertan, A.; Jiang, N. Y.; Rice, J. C.; Sbeiti, M.; Rossowski, Wojciech J.; Coy, D. H.
CORPORATE SOURCE: Sch. Med., Tulane Univ., New Orleans, LA, 70112, USA
SOURCE: Peptides (Fayetteville, N. Y.) (1991), 12(4), 749-53
CODEN: PPTDD5; ISSN: 0196-9781
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Bombesin (BN) analogs designed to be competitive receptor antagonists at the BN/gastrin releasing peptide receptor(s) can exhibit diverse properties ranging from full antagonist, partial agonist or weak agonist activity, depending on the assay system and animal species employed. The following 3 antagonists which have the most potent receptor affinities in several in vitro assay systems and are representative of 3 main classes of BN antagonists for their in vivo effects on pancreatic amylase secretion in the rat were evaluated: [D-Cpa6, Phe14, .psi.13-14]BN(6-14), [D-Phe6]BN(6-13) propylamide, and [D-Phe6]BN(6-13) Me ester. After injection in the rat, the Me ester was clearly the most potent antagonist and completely inhibited BN-stimulated amylase release at the 20 nmol/kg (IV bolus) for .apprx.2 h. In contrast, the propylamide analog at the 200 nmol/kg (i.v. bolus) dose produced incomplete inhibition of amylase release. Inhibition was transient and lasted for only .apprx.1 h, possibly reflecting the significant agonist activity of this latter peptide in the rat pancreatic amylase secretion test in vitro. The .psi.-analog, while being the longest acting analog, was also incapable of lowering amylase to basal level at 50 times the BN dose, suggesting that it is a mixed agonist-antagonist in vivo as was also previously shown in vitro in the rat.

IT **124199-91-3 130800-38-3**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(bombesin agonist and antagonist activity of)

L24 ANSWER 38 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:550746 HCAPLUS
DOCUMENT NUMBER: 115:150746
TITLE: Covalently cyclized agonist and antagonist analogs of bombesin and related peptides
AUTHOR(S): Coy, David H.; Jiang, Ning Yi; Kim, Sun Hyuk; Moreau, Jacques Pierre; Lin, Jaw Town; Frucht, Harold; Qian, Jia Ming; Wang, Lu Wa; Jensen, Robert T.
CORPORATE SOURCE: Med. Cent., Tulane Univ., New Orleans, LA, 70112, USA
SOURCE: J. Biol. Chem. (1991), 266(25), 16441-8
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB During a search for possible cyclization points in shortened, potent bombesin agonists and antagonists, it was found that the joining of amino acid residues in positions 6 and 14 by various means resulted in retention of significant binding affinity for rat pancreatic acini and murine Swiss 3T3 cells. In one series of analogs, Cys residues in these positions were used for bridging via a disulfide bond. (D)-C-Q-W-A-V-G-H-L-C-NH2 retained significant binding affinity for rat pancreatic acini cells and was a full amylase releasing agonist (EC50 187 nM). Potency was markedly increased by substituting D-Ala for Gly (EC50 67 nM compared to 10 nM for its linear counterpart) and was decreased by substituting L-Cys for D-Cys in this analog (EC50 214 nM), thus strongly suggesting stabilization of peptide folding by the D residues. Elimination of the COOH-terminal amino acid produces competitive antagonists in the linear analogs; however, (D)-C-Q-W-A-V-G-H-C-NH2 was devoid of activity. Likewise, cyclization to position 13 with the 14 amino acids intact to give (D)-C-Q-W-A-V-G-H-C-L-NH2 resulted in an almost inactive peptide. On the other hand, as in the linear series, the reduced peptide bond analog, (D)-C-Q-W-A-V-(D)-A-H-L-.psi.(CH2NH)-C-NH2, was a receptor antagonist (IC50 5.7 mM), albeit much weaker than the corresponding linear analogs, but with no residual agonist activity. Direct head-to-tail cyclization was also tried. Both cycle[(D)-F-Q-W-A-V-G-H-L-L] (EC50 346 nM) and the shorter cyclo[Q-W-A-V-G-H-L-L] (EC50 1236 nM) were full agonists. Elimination of the COOH-terminal residue in cyclo[(D)-p-Cl-F-Q-W-A-V-(D)-A-H-L] produced an agonist (EC50 716 nM) rather than an antagonist. These results provide support for the proposal that both bombesin agonists and antagonists adopt a folded conformation at their receptor(s). Furthermore, the retention of appreciable potencies using several cyclization strategies and chain lengths suggests that further optimization of these structures both in terms of potency and ring size is possible. Since these peptides have increased conformational restriction, they should begin to serve as useful substrates for NMR and mol. modeling studies aimed at comparing the obviously subtle differences between agonist and antagonist structures.

IT **124176-13-2**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(biol. activity of, mol. structure in relation to)

L24 ANSWER 39 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:550377 HCAPLUS
DOCUMENT NUMBER: 115:150377
TITLE: Therapeutic peptide analogs of bombesin or gastrin-releasing peptide
INVENTOR(S): Coy, David H.; Moreau, Jacques Pierre; Kim, Sun Hyuk
PATENT ASSIGNEE(S): Biomeasure, Inc., USA; Tulane Educational Fund, Inc.
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9102746	A1	19910307	WO 1990-US4646	19900817
W: AU, CA, FI, JP, NO				
RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
US 5084555	A	19920128	US 1990-502438	19900330
CA 2064896	AA	19910222	CA 1990-2064896	19900817
AU 9062940	A1	19910403	AU 1990-62940	19900817
AU 648037	B2	19940414		
EP 489089	A1	19920610	EP 1990-913117	19900817
EP 489089	B1	19960619		
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE				
JP 04506664	T2	19921119	JP 1990-512265	19900817
AT 139540	E	19960715	AT 1990-913117	19900817
ES 2090140	T3	19961016	ES 1990-913117	19900817
NO 9200678	A	19920406	NO 1992-678	19920220

PRIORITY APPLN. INFO.:

US 1989-397169	A	19890821
US 1990-502438	A	19900330
US 1987-100571	B2	19870924
US 1988-173311	B2	19880325
US 1988-204171	B2	19880608
US 1988-207759	B2	19880616
US 1988-248771	B2	19880923
US 1988-257998	B2	19881014
US 1988-282328	A2	19881209
US 1989-317941	B2	19890302
US 1989-376555	B2	19890707
WO 1990-US4646	A	19900817

OTHER SOURCE(S): MARPAT 115:150377

AB Linear peptide analogs of biol. active bombesin or mammalian gastrin-releasing peptide (GRP) have (a) a deletion of an amino acid residue within the active site and a modification of an amino acid residue outside of the active site; (b) a replacement of 2 amino acid residues within the active site with a synthetic amino acid, a .beta.-amino acid, or a .gamma.-amino acid residue; or (c) a nonpeptide bond instead of a peptide bond between an amino acid residue of the active site and an adjacent amino acid residue. Preferably, the analog is capable of acting as a competitive inhibitor of the naturally-occurring peptide. BIM-26100 [pGlu-Gln-Trp-Ala-Val-Gly-His-Phe.psi.[CH2NH]Leu-NH2 (pGlu-pyroglutamic acid; .psi.[CH2NH] = nonpeptide bond)] inhibited binding of 125I-labeled GRP to 3T3 fibroblast bombesin receptors and bombesin-stimulated [3H]thymidine uptake by cultured 3T3 cells with IC50 values of 23 and 26 nm, resp. BIM-26100 inhibited NCI-H69 small-cell lung carcinoma cells. Synthesis of litorin and bombesin analogs using benzhydrylamine-polystyrene resin is described.

IT **124176-07-4**
RL: BIOL (Biological study)
(as litorin analog, gastrin-releasing peptide receptor response to)

IT **124176-07-4P 124176-08-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as therapeutic bombesin antagonist)

L24 ANSWER 40 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:485834 HCAPLUS

DOCUMENT NUMBER: 115:85834
TITLE: Effects of potent bombesin antagonist on exocrine pancreatic secretion in rats
AUTHOR(S): Varga, Gabor; Reidelberger, Roger D.; Liehr, Ralf Marco; Bussjaeger, Louis J.; Coy, David H.; Solomon, Travis E.
CORPORATE SOURCE: Med. Cent., Kansas Univ., Kansas City, KS, 66103, USA
SOURCE: Peptides (Fayetteville, N. Y.) (1991), 12(3), 493-7
CODEN: PPTDD5; ISSN: 0196-9781
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recent synthesis of specific, potent bombesin receptor antagonists allows examn. of the role of bombesin-like peptides in physiol. processes in vivo. The effects of [D-Phe6]bombesin(6-13)-methyl-ester (BME) on pancreatic enzyme secretion stimulated by the C-terminal decapeptide of gastrin releasing peptide (GRP-10), food intake, and diversion of bile-pancreatic juice in rats were characterized. In isolated pancreatic acini, BME had no agonistic effects on amylase secretion but competitively inhibited responses to GRP-10, yielding a pA2 value of 8.89. In conscious rats with gastric, jugular vein, bile-pancreatic, and duodenal cannulas, basal enzyme secretion (bile-pancreatic juice recirculated) was not affected by the antagonist. Maximal amylase response to GRP-10 (0.5 nmol/kg/h) was inhibited dose dependently by BME, reaching 97% inhibition at a dose of 400 nmol/kg/h. The dose response curve of amylase secretion stimulated by GRP-10 was shifted to the right by 40 nmol/kg/h BME, but maximal amylase response was unaltered, suggesting competitive inhibition in vivo. Liq. food intake and bile-pancreatic juice diversion caused substantial increases in amylase secretion; neither response was altered during administration of 400 pmol/kg/h BME. These results demonstrate that BME is a potent, competitive antagonist of pancreatic responses to bombesin-like peptides in vitro and in vivo. Lack of effect of BME on basal pancreatic secretion or responses to liq. food intake or diversion of bile-pancreatic juice in rats suggests that endogenous bombesin-like peptides do not act either directly or indirectly to mediate these responses.

IT **130800-38-3**
RL: BIOL (Biological study)
(pancreatic secretion stimulation by gastrin-releasing peptide inhibition by)

L24 ANSWER 41 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:422710 HCAPLUS
DOCUMENT NUMBER: 115:22710
TITLE: Gastrin-releasing peptide is a transmitter mediating porcine gallbladder contraction
AUTHOR(S): Schjoldager, Birgit; Poulsen, Steen Seier; Schmidt, Peter; Coy, David H.; Holst, Jens Juul
CORPORATE SOURCE: Panum Inst., Univ. Copenhagen, Copenhagen, 2200, Den.
SOURCE: Am. J. Physiol. (1991), 260(4, Pt. 1), G577-G585
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The role of gastrin-releasing peptide (GRP) in porcine gallbladder motility was detd. Immunohistochem. visualized nerve fibers contg. GRP-like immunoreactivity in muscularis. GRP concn. dependently stimulated contractions of muscularis strips (ED50, 2.9 nM). Neuromedin B was less potent (ED50, 0.1 .mu.M), suggesting existence of GRP-preferring receptors. GRP-induced contractions were unaffected by muscarinic antagonism (1 .mu.M atropine), axonal blockade (1 .mu.M tetrodotoxin), CCK

receptor antagonism (10 .mu.M MK-329), or substance P desensitization (1 .mu.M), supporting the existence of myogenic GRP receptors. The bombesin (BN) analog D-Phe6-BN-(6-13)propylamide (PA) stimulated contractions (ED50, 3.3 nM) with low efficacy (29% of that of GRP). D-Phe6-BN-(6-13)PA (1 .mu.M) shifted GRP concn.-response curves one log to the right. D-Phe6-BN-(6-13)PA interacted specifically with GRP receptors; while abolishing responses to GRP (1 nM); responses to substance P (0.1 .mu.M) and CCK-8 (1 nM) were unchanged. Elec. stimulation (10 Hz, 0.5 ms, 10 V) caused a rapid onset-flow offset, tetrodotoxin-sensitive excitation. Atropine reduced the amplitude to 58% and caused a delayed, slow onset-slow decline response. D-Phe6-BN-(6-13)PA reduced the amplitude to 59% and caused a very rapid onset-rapid decline response. Atropine plus D-Phe6-BN-(6-13)PA abolished responses to nerve stimulation. Nerve stimulation released GRP-like immunoreactivity. Thus, 2 neural inputs were defined: a cholinergic rapid onset-rapid offset excitation and a delayed, slow onset-flow offset excitation caused by release and subsequent binding of GRP to GRP-preferring receptors.

IT **124199-91-3**
RL: BIOL (Biological study)
(gastrin releasing peptide mediation of gallbladder contraction inhibition by)

L24 ANSWER 42 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:178480 HCAPLUS
DOCUMENT NUMBER: 114:178480
TITLE: [Des-Met14]bombesin analogs function as small cell lung cancer bombesin receptor antagonists
AUTHOR(S): Staley, J.; Coy, D.; Taylor, J. E.; Kim, S.; Moody, Terry W.
CORPORATE SOURCE: Sch. Med. Health Sci., George Washington Univ., Washington, DC, 20037, USA
SOURCE: Peptides (Fayetteville, N. Y.) (1991), 12(1), 145-9
CODEN: PPTDD5; ISSN: 0196-9781
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of bombesin (BN) analogs lacking the C-terminal methionine at the 14 position were evaluated as BN receptor antagonists. [D-Phe6]BN(6-13)amide inhibited specific 125I-GRP binding to lung cancer cell line NCI-H720 with an IC50 value of 12 nM. In contrast, [D-Phe6]BN(6-13)propylamide, butylamide, and Me ester were more potent with IC50 values of 3, 5, and 5 nM whereas [D-Phe6,Sta13]BN(6-13)amide was less potent with an IC50 value of 180 nM. [D-Phe6]BN(6-13)propylamide antagonized the ability of BN to elevate cytosolic Ca2+, whereas [D-Phe6]BN(6-13)butylamide was a partial agonist. In a small cell lung cancer (SCLC) growth assay, [D-Phe6]BN(6-13) propylamide inhibited colony formation. In summary, BN analogs which lack a C-terminal methionine may function as useful SCLC BN receptor antagonists.
IT **124176-07-4 124199-91-3 130800-27-0 130800-38-3**
RL: BIOL (Biological study)
(bombesin receptor antagonism by, in small cell lung cancer)

L24 ANSWER 43 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:886 HCAPLUS
DOCUMENT NUMBER: 114:886
TITLE: Potent bombesin receptor antagonists distinguish receptor subtypes
AUTHOR(S): Von Schrenck, T.; Wang, L. H.; Coy, D. H.; Villanueva, M. L.; Mantey, S.; Jensen, R. T.

CORPORATE SOURCE: Dig. Dis. Branch, Natl. Inst. Diabetes Dig. Kidney Dis., Bethesda, MD, 20892, USA
SOURCE: Am. J. Physiol. (1990), 259(3, Pt. 1), G468-G473
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To det. whether bombesin (BN) receptor antagonists distinguish subtypes of BN receptors, their abilities to interact with BN receptors on esophageal muscle or pancreatic acinar tissue were examd. For inhibition of binding of 125I-[Tyr4]BN to rat pancreatic tissue, the relative potencies were [D-Phe6]BN-(6-13)ethyl ester (5 nM) > Ac-gastrin-releasing peptide (GRP)-(20-26)ethyl ester (17 nM) > [D-Phe6,Cpa14,.psi.13-14]BN-(6-14) (40 nM) > [Leu14,.psi.13-14]BN (0.43 .mu.M) > [Tyr4, D-Phe12]BN = [D-Pro4,D-Trp7,9,10]substance P(SP)-4-11 (13 .mu.M) > [Leu14,.psi.9,10]BN (32 M.mu.) > [D-Arg1,D-Trp7,9,Leu11]SP (70 .mu.M). Each antagonist also inhibited binding of 125I-[Tyr4]BN or 125I-Bolton-Hunter-neuromedin B to rat esophageal tissue, and the potency of each antagonist for each tracer was similar. In comparison to rat pancreas [D-Phe6]BN-(6-13)ethyl ester, Ac-GRP-(20-26)ethyl ester, [D-Phe6,Cpa14, .psi.13-14]BN-(6-14), [Leu14,.psi.13-14]BN, and [Leu14,.psi.9,10]-BN had a 10,000-, 2940-, 1425-, 122-, and 4-fold, resp., weaker affinity for BN receptors. In contrast [Tyr4,D-Ph12]-BN, [D-Pro4,D-Trp7,9,10]SP-4-11, and [D-Arg1,D-Trp7,9,Leu11]-SP had a 4-, 4-, and 9-fold, resp., higher affinity compared with pancreatic tissue. Comparison of the activity of each peptide at inhibiting the ability of equipotent concns. of BN or neuromedin B to stimulate contraction of rat esophageal muscle demonstrated that each peptide had the same relative potencies as for inhibiting binding. Each peptide also had the same relative inhibitor potencies for inhibiting BN-stimulated amylase release from dispersed pancreatic acini as for inhibiting binding to pancreatic tissue except for the 2 SP analogs, which had agonist activity in rat pancreas. These results demonstrate that different subtypes of BN receptors can be easily distinguished by these various classes of receptor antagonists.

IT **124199-90-2**
RL: BIOL (Biological study)
(gastrin-releasing peptide receptors of esophagus and pancreas differentiation by)

L24 ANSWER 44 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:673 HCAPLUS
DOCUMENT NUMBER: 114:673
TITLE: Des-Met carboxyl-terminally modified analogs of bombesin function as potent bombesin receptor antagonists, partial agonists, or agonists
AUTHOR(S): Wang, Lu Hua; Coy, David H.; Taylor, John E.; Jiang, Ning Yi; Moreau, Jacques Pierre; Huang, Shih Che; Frucht, Harold; Haffar, Bassam M.; Jensen, Robert T.
CORPORATE SOURCE: Dig. Branch, Natl. Inst. Diabetes Dig. Kidney Dis., Bethesda, MD, 20892, USA
SOURCE: J. Biol. Chem. (1990), 265(26), 15695-703
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of carboxyl-terminal modifications of des-Met14-bombesin (Bn) on Bn receptor affinity in murine 3T3 cells, rat and guinea pig pancreatic acini, and the ability to initiate biol. responses were examd. by synthesizing 18 des-Met14-Bn(6-13) analogs. With guinea pig acini and cells, affinity was affected by the chain lengths of the alkyl moiety (R) added to [D-Phe6]Bn(6-13)NH2R with relative potencies: Pr > Et > Bu =

hexyl > heptyl > free amide, whereas in rat acini affinity was not increased by the chain length. In each cell system the affinity of the alkylamide was not increased by insertion of a Ph group in the alkyl side chain, by making the analog more neuromedin B-like, or by addn. of a reduced peptide bond. The affinity in each cell system was increased by addns. of other electron releasing groups to the COOH-terminal carboxyl group such as [D-Phe6]Bn(6-13)ethyl or Me ester, or hydrazide. In guinea pig pancreas and 3T3 cells, 12 analogs were antagonists, 1 a full and 5 partial agonists. In rat pancreas, 8 were antagonists, 5 full agonists, and 5 partial agonists. Potent antagonists in each cell system were the Me and Et ester, hydrazide, and ethylamide analogs. In 3T3 cells or guinea pig pancreas, agonist activity of the alkylamide was critically dependent on the chain length, whereas with rat pancreatic Bn receptors any alkylamide longer than the ethylamide had agonist activity. In all 3 cell systems any alteration that made the alkylamide more neuromedin B-like caused agonist activity. Thus, the nature of the substitution on the carboxyl terminus of des-Met14-Bn analog is critically important, not only for detg. Bn receptor affinity, but also for detg. the ability to initiate a biol. response. Evidently, the presence of the COOH-terminal amino acid in position 14 of Bn is not essential for initiating a biol. response. Several des-Met14-Bn analogs were potent partial agonists, whereas others such as the hydrazide or Et ester are very potent antagonists.

IT **124176-07-4 124199-90-2 124199-91-3**
130800-27-0 130800-28-1 130800-29-2
130800-30-5 130800-31-6 130800-36-1
130800-37-2 130800-38-3 130800-39-4
130832-65-4
RL: BIOL (Biological study)
(bombesin receptor agonist and antagonist activity of, mol. structure in relation to)

L24 ANSWER 45 OF 46 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1990:572755 HCAPLUS
DOCUMENT NUMBER: 113:172755
TITLE: Peptide hormone antagonists for treatment of tumors and gastrointestinal disorders
INVENTOR(S): Coy, David H.; Moreau, Jacques Pierre; Taylor, John E.; Kim, Sun Hyuk
PATENT ASSIGNEE(S): Tulane Educational Fund, Inc., USA
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9003980	A1	19900419	WO 1989-US4616	19891013
W: AU, BB, BG, BR, DK, FI, HU, JP, KP, KR, LK, MC, MG, MW, NO, RO, SD, SU				
RW: AT, BE, BF, BJ, CF, CG, CH, CM, DE, FR, GA, GB, IT, LU, ML, MR, NL, SE, SN, TD, TG				
US 5162497	A	19921110	US 1988-282328	19881209
AU 8944949	A1	19900501	AU 1989-44949	19891013
AU 638423	B2	19930701		
EP 438519	A1	19910731	EP 1989-912292	19891013
EP 438519	B1	19980506		

R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

HU 59420	A2	19920528	HU 1991-63	19891013
JP 04504406	T2	19920806	JP 1989-511442	19891013
JP 2919889	B2	19990719		
RU 2088592	C1	19970827	RU 1989-4895537	19891013
AT 165836	E	19980515	AT 1989-912292	19891013
CA 2008454	AA	19900902	CA 1990-2008454	19900124
DK 9100663	A	19910614	DK 1991-663	19910412

PRIORITY APPLN. INFO.:

US 1988-257998	A	19881014
US 1988-282328	A	19881209
US 1989-317941	A	19890302
US 1989-376555	A	19890707
US 1989-397169	A	19890821
US 1987-100571	B2	19870924
US 1988-173311	B2	19880325
US 1988-204171	B2	19880608
US 1988-207759	B2	19880616
US 1988-248771	B2	19880923
WO 1989-US4616	A	19891013

OTHER SOURCE(S): MARPAT 113:172755

AB Linear peptide analogs of amphibian bombesin or mammalian gastrin-releasing peptide, e.g., R1R2A0-A1-A2-Trp-A4-A5-A6-A7-W [A0 = Gly, Nle, .alpha.-aminobutyric acid residue, D-Ala, D-Val, D-Gln, D-Asn, null, etc.; A1 = D- or L-pGlu, Nle, .alpha.-aminobutyric acid residue, D-Ala, D-Val, D-Gln, D-Asn, null, etc.; A2 = pGlu, Gly, Ala, Val, Gln, Asn, Leu, Ile, Met, Trp, Cys, .beta.-Nal, His, etc.; A4 = Ala, Val, Gln, Asn, Gly, Leu, Ile, Nle, .alpha.-aminobutyric acid residue, Met, Trp, Cys, .beta.-val; A5 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, .alpha.-aminobutyric acid residue, Met, Val, Trp, Thr, .beta.-Val; A6 = Ser, Gly, D-Ala, D-Val, D-Gln, D-Asn, D-Leu, D-Ile, D-Met, D-Trp, D-Cys, D-.beta.-val; A7 = His(1- or 3-Me); W = NHCH(Z1)XCOV Z1 = amino acid residue; X = null, (hydroxy)ethylene; V = alkoxy, PhO, naphthyloxy, amino, etc.; when A0 = null, and A1 = pGlu, then R1 = H; R2 = atoms forming the imine ring of pGlu], were prepd. as competitive inhibitors of the natural peptide. Thus, H-pGlu-Gln-Trp-Ala-Val-Gly-His-Phe.PSI.[CH2NH]Leu-NH2, prepd. by the solid phase method, at 50 .mu.g s.c. in mice limited the size of NCI-H69 SCLC tumors to 86% of controls after 28 days.

IT **124176-07-4P 124176-08-5P 124199-90-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, for treatment of tumors and gastrointestinal disorders)

L24 ANSWER 46 OF 46 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1990:132551 HCAPLUS

DOCUMENT NUMBER: 112:132551

TITLE: Desmethionine alkylamide bombesin analogs: a new class of bombesin receptor antagonists with potent antisecretory activity in pancreatic acini and antimitotic activity in Swiss 3T3 cells

AUTHOR(S): Wang, Lu Hua; Coy, David H.; Taylor, John E.; Jiang, Ning Yi; Kim, Sun Hyuk; Moreau, Jacques Pierre; Huang, Shih Che; Mantey, Samuel A.; Frucht, Harold; Jensen, Robert T.

CORPORATE SOURCE: Dig. Dis. Branch, Natl. Inst. Diabetes Dig. Kidney Dis., Bethesda, MD, 20892, USA

SOURCE: Biochemistry (1990), 29(3), 616-22
CODEN: BICHAW; ISSN: 0006-2960

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Twenty-one des-Met amide or alkylamide analogs of bombesin (Bn) were

synthesized and their abilities to function as bombesin receptor antagonists in guinea pig pancreatic acini and Swiss 3T3 cells were compared with those of the previously most potent antagonist described, [Leu13.psi.(CH2NH)Leu14]bombesin (I). All des-Met analogs functioned as antagonists. Bn(1-13)NH2 was approx. equipotent to I (Ki = 60-80 nM) whereas Bn(6-13)NH2 was 30-fold less potent (Ki = 1800 nM). Formation of an ethylamide, Bn(6-13)ethylamide, increased the potency 30-fold such that this octapeptide was equipotent to I. The addn. of a D-Phe6 moiety to I did not change potency but caused a 30-fold increase in potency of Bn(6-13)NH2, and a 8-fold increase in the potency of Bn(6-13)ethylamide (Ki = 16 nM). Addnl. studies of both NH2- and COOH-terminal alterations in Bn(6-13)NH2 demonstrated that the most potent antagonist was [D-Phe6]Bn(6-13)propylamide (PA), having IC50's of 1.6 nM and 0.8 nM for bombesin-stimulated amylase release and Swiss 3T3 cell growth, resp. Detailed studies of the most potent amide analog, [D-Phe6]Bn(6-13)NH2, and the alkylamide analog, [D-Phe6]Bn(6-13)PA, demonstrated that these analogs functioned as competitive antagonists and that their action was selective for the bombesin receptor. Thus, as with cholecystokinin- and gastrin-related peptides, the C-terminal amino acid is important for initiating a biol. response but not essential for detg. receptor affinity. Furthermore, the most potent des-Met analog, [D-Phe6]Bn(6-13)PA, is 30-fold more potent than any previously described bombesin receptor antagonist. This member of this new class of antagonists can be easily synthesized, offers fewer proteolytic degrdn. sites, and should be useful for in vivo studies.

IT **124176-07-4P 124176-08-5P 124176-13-2P**
124199-86-6P 124199-90-2P 124199-91-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and bombesin receptor antagonist activity of, structure in relation to)

```
=> fil re
'RE' IS AN AMBIGUOUS FILE OR CLUSTER NAME
 REACTION          - Reactions Cluster
 RESEARCH          - Research Cluster
 REGISTRY          - The CAS Registry File of substances
ENTER FILE OR CLUSTER NAME (IGNORE):reg
FILE 'REGISTRY' ENTERED AT 15:34:12 ON 26 OCT 2001
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2001 American Chemical Society (ACS)

STRUCTURE FILE UPDATES:   25 OCT 2001  HIGHEST RN 364728-23-4
DICTIONARY FILE UPDATES:  25 OCT 2001  HIGHEST RN 364728-23-4

TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER see
HELP CROSSOVER for details.

Calculated physical property data is now available.  See HELP PROPERTIES
for more information.  See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf
```

```
=>
=>

=> d .seq l23 1-41

L23  ANSWER 1 OF 41  REGISTRY  COPYRIGHT 2001 ACS
RN   357176-83-1  REGISTRY
CN   INDEX NAME NOT YET ASSIGNED
OTHER NAMES:
CN   12: PN: WO0162777 SEQID: 12 claimed protein
NTE  modified
----------------------------------------------------------------------
 type            ------ location ------         description
----------------------------------------------------------------------
uncommon         Aib-6           -         -
modification     Phe-1           -         1-oxooctyl<Oct>
----------------------------------------------------------------------
SQL  8
FS   PROTEIN SEQUENCE; STEREOSEARCH
SQL  8

SEQ      1 FQWAVXHL
           ========
HITS AT:   1-8

REFERENCE   1:  135:190403

L23  ANSWER 2 OF 41  REGISTRY  COPYRIGHT 2001 ACS
RN   357176-70-6  REGISTRY
CN   INDEX NAME NOT YET ASSIGNED
OTHER NAMES:
CN   11: PN: WO0162777 SEQID: 11 claimed protein
NTE  modified
----------------------------------------------------------------------
 type            ------ location ------         description
----------------------------------------------------------------------
uncommon         Aib-6           -         -
modification     Phe-1           -         undetermined modification
----------------------------------------------------------------------
SQL  8
FS   PROTEIN SEQUENCE; STEREOSEARCH
SQL  8

SEQ      1 FQWAVXHL
           ========
HITS AT:   1-8

REFERENCE   1:  135:190403

L23  ANSWER 3 OF 41  REGISTRY  COPYRIGHT 2001 ACS
RN   357176-55-7  REGISTRY
CN   L-Leucine, D-phenylalanyl-L-glutaminyl-L-tryptophyl-2-amino-2-
     ethylbutanoyl-L-valylglycyl-L-histidyl- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   9: PN: WO0162777 SEQID: 9 claimed protein
NTE
----------------------------------------------------------------------
 type            ------ location ------         description
----------------------------------------------------------------------
```

uncommon Aaa-4 - -
stereo Phe-1 - D

SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWXVGHL
========
HITS AT: 1-8

REFERENCE 1: 135:190403

L23 ANSWER 4 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 357176-08-0 REGISTRY
CN L-Isoleucine, D-phenylalanyl-L-glutaminyl-L-tryptophyl-L-alanyl-L-valyl-2-methylalanyl-L-histidyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 7: PN: WO0162777 SEQID: 7 claimed protein
NTE

---

type ------ location ------ description

---

uncommon Aib-6 - -

SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVXHI
========
HITS AT: 1-8

REFERENCE 1: 135:190403

L23 ANSWER 5 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 357175-80-5 REGISTRY
CN L-Isoleucine, D-phenylalanyl-L-glutaminyl-L-tryptophyl-2-methylalanyl-L-valylglycyl-L-histidyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 6: PN: WO0162777 SEQID: 6 claimed protein
NTE

---

type ------ location ------ description

---

uncommon Aib-4 - -

SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWXVGHI
========
HITS AT: 1-8

REFERENCE 1: 135:190403

L23 ANSWER 6 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 357175-71-4 REGISTRY

CN L-Leucine, D-phenylalanyl-L-glutaminyl-D-tryptophyl-L-alanyl-L-valyl-2-methylalanyl-L-histidyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 5: PN: WO0162777 SEQID: 5 claimed protein
CN 8: PN: WO0162777 SEQID: 8 claimed protein
NTE

type	------ location ------		description
uncommon	Aib-6	-	-

SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVXHL
========
HITS AT: 1-8

REFERENCE 1: 135:190403

L23 ANSWER 7 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 357175-69-0 REGISTRY
CN L-Leucine, D-phenylalanyl-L-glutaminyl-L-tryptophyl-2-methylalanyl-L-valylglycyl-L-histidyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 4: PN: WO0162777 SEQID: 4 claimed protein
NTE

type	------ location ------		description
uncommon	Aib-4	-	-

SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWXVGHL
========
HITS AT: 1-8

REFERENCE 1: 135:190403

L23 ANSWER 8 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 357175-68-9 REGISTRY
CN L-Leucine, D-phenylalanyl-L-glutaminyl-L-tryptophyl-L-alanyl-L-valyl-2-methylalanyl-L-histidyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 10: PN: WO0162777 SEQID: 10 claimed protein
CN 11: PN: WO0162777 SEQID: 11 claimed protein
CN 12: PN: WO0162777 SEQID: 12 claimed protein
CN 3: PN: WO0162777 SEQID: 3 claimed protein
NTE

type	------ location ------		description
uncommon	Aib-6	-	-

SQL 8

FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVXHL
========
HITS AT: 1-8

REFERENCE 1: 135:190403

L23 ANSWER 9 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 309246-58-0 REGISTRY
CN L-Leucine, L-phenylalanyl-L-glutaminyl-L-tryptophyl-L-alanyl-L-valylglycyl-L-histidyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 400: PN: WO0069900 SEQID: 1086 unclaimed sequence
SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 134:21425

L23 ANSWER 10 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 288570-89-8 REGISTRY
CN L-Isoleucinamide, D-phenylalanyl-L-glutaminyl-L-tryptophyl-L-alanyl-L-valyl-2-methylalanyl-L-histidyl- (9CI) (CA INDEX NAME)
NTE modified

type	------ location ------		description
terminal mod.	Ile-8	-	C-terminal amide
uncommon	Aib-6	-	-

SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVXHI
========
HITS AT: 1-8

REFERENCE 1: 133:198647

L23 ANSWER 11 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 288570-87-6 REGISTRY
CN L-Isoleucinamide, D-phenylalanyl-L-glutaminyl-L-tryptophyl-2-methylalanyl-L-valylglycyl-L-histidyl- (9CI) (CA INDEX NAME)
NTE modified

type	------ location ------		description
terminal mod.	Ile-8	-	C-terminal amide
uncommon	Aib-4	-	-

SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH

SQL 8

SEQ 1 FQWXVGHI
========
HITS AT: 1-8

REFERENCE 1: 133:198647

L23 ANSWER 12 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 288570-85-4 REGISTRY
CN L-Leucinamide, D-phenylalanyl-L-glutaminyl-L-tryptophyl-L-alanyl-L-valyl-2-methylalanyl-L-histidyl- (9CI) (CA INDEX NAME)
NTE modified

type	------ location ------		description
terminal mod.	Leu-8	-	C-terminal amide
uncommon	Aib-6	-	-

SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVXHL
========
HITS AT: 1-8

REFERENCE 1: 133:198647

L23 ANSWER 13 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 288570-83-2 REGISTRY
CN L-Leucinamide, D-phenylalanyl-L-glutaminyl-L-tryptophyl-2-methylalanyl-L-valylglycyl-L-histidyl- (9CI) (CA INDEX NAME)
NTE modified

type	------ location ------		description
terminal mod.	Leu-8	-	C-terminal amide
uncommon	Aib-4	-	-

SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWXVGHL
========
HITS AT: 1-8

REFERENCE 1: 133:198647

L23 ANSWER 14 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 283178-52-9 REGISTRY
CN L-Leucinamide, N-[4-(fluoro-18F)benzoyl]-D-phenylalanyl-L-glutaminyl-L-tryptophyl-L-alanyl-L-valylglycyl-L-histidyl-N-ethyl- (9CI) (CA INDEX NAME)
NTE modified

type	------ location ------		description

modification Phe-1 - undetermined modification

SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 133:105330

L23 ANSWER 15 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 283178-50-7 REGISTRY
CN L-Leucinamide, N-(4-fluorobenzoyl)-D-phenylalanyl-L-glutaminyl-L-tryptophyl-L-alanyl-L-valylglycyl-L-histidyl-N-ethyl- (9CI) (CA INDEX NAME)
NTE modified

type	------ location ------		description
modification	Phe-1	-	undetermined modification

SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 133:105330

L23 ANSWER 16 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 244168-25-0 REGISTRY
CN L-Leucinamide, D-phenylalanyl-L-glutaminyl-L-tryptophyl-L-alanyl-L-valylglycyl-L-histidyl-N-[(1S)-2-hydroxy-4-methyl-1-(2-methylpropyl)pentyl]- (9CI) (CA INDEX NAME)
NTE modified
SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 131:243570

L23 ANSWER 17 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 229626-64-6 REGISTRY
CN L-Leucine, D-phenylalanyl-L-glutaminyl-L-tryptophyl-L-alanyl-L-valylglycyl-L-histidyl-, 2,2-dimethylhydrazide (9CI) (CA INDEX NAME)
NTE modified
SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVGHL

```
           ========
HITS AT:   1-8

REFERENCE   1:  131:83232

L23  ANSWER 18 OF 41  REGISTRY  COPYRIGHT 2001 ACS
RN   227624-59-1  REGISTRY
CN   L-Leucinamide, N-[(1,1-dimethylethoxy)carbonyl]-D-phenylalanyl-L-
     glutaminyl-L-tryptophyl-L-alanyl-L-valylglycyl-L-histidyl-N-
     (phenylmethoxy)- (9CI)  (CA INDEX NAME)
NTE  modified
----------------------------------------------------------------------
 type            ------ location ------         description
----------------------------------------------------------------------
modification     Phe-1           -         (1,1-dimethylethoxy) carbonyl<Boc>
----------------------------------------------------------------------
SQL  8
FS   PROTEIN SEQUENCE; STEREOSEARCH
SQL  8

SEQ      1 FQWAVGHL
           ========
HITS AT:   1-8

REFERENCE   1:  131:45089

L23  ANSWER 19 OF 41  REGISTRY  COPYRIGHT 2001 ACS
RN   215532-61-9  REGISTRY
CN   L-Leucinamide, D-phenylalanyl-L-glutaminyl-L-tryptophyl-L-alanyl-L-
     valylglycyl-L-histidyl-N-(phenylmethoxy)- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   JMV 1459
NTE  modified
SQL  8
FS   PROTEIN SEQUENCE; STEREOSEARCH
SQL  8

SEQ      1 FQWAVGHL
           ========
HITS AT:   1-8

REFERENCE   1:  131:45089

REFERENCE   2:  129:339929

L23  ANSWER 20 OF 41  REGISTRY  COPYRIGHT 2001 ACS
RN   215532-60-8  REGISTRY
CN   L-Leucinamide, D-phenylalanyl-L-glutaminyl-L-tryptophyl-L-alanyl-L-
     valylglycyl-L-histidyl-N-hydroxy- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   JMV 1449
NTE  modified
SQL  8
FS   PROTEIN SEQUENCE; STEREOSEARCH
SQL  8

SEQ      1 FQWAVGHL
           ========
HITS AT:   1-8
```

REFERENCE 1: 131:45089

REFERENCE 2: 129:339929

L23 ANSWER 21 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 163759-33-9 REGISTRY
CN 3-9-Ranatensin, 3-(4-chloro-D-phenylalanine)-9-[N-[1-[[4-(aminocarbonyl)-2,2-dimethyl-3-thiazolidinyl]methyl]-3-methylbutyl]-L-histidinamide]-, [R-(R*,S*)]- (9CI) (CA INDEX NAME)
NTE modified (modifications unspecified)

type	------ location ------		description
stereo	Phe-1	-	D

SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 123:9930

L23 ANSWER 22 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 163759-32-8 REGISTRY
CN 3-9-Ranatensin, 3-(N-acetyl-D-phenylalanine)-9-[N-[1-[[4-(aminocarbonyl)-2,2-dimethyl-3-thiazolidinyl]methyl]-3-methylbutyl]-L-histidinamide]-, [R-(R*,S*)]- (9CI) (CA INDEX NAME)
NTE modified (modifications unspecified)

type	------ location ------		description
stereo	Phe-1	-	D

SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 123:9930

L23 ANSWER 23 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 163759-31-7 REGISTRY
CN 3-9-Ranatensin, 3-D-phenylalanine-9-[N-[1-[[4-(aminocarbonyl)-2,2-dimethyl-3-thiazolidinyl]methyl]-3-methylbutyl]-L-histidinamide]-, [R-(R*,S*)]- (9CI) (CA INDEX NAME)
NTE modified (modifications unspecified)

type	------ location ------		description
stereo	Phe-1	-	D

SQL 8

FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 123:9930

L23 ANSWER 24 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 163759-21-5 REGISTRY
CN 3-9-Ranatensin, 3-(N-acetyl-D-phenylalanine)-9-[N-[1-[[4-(aminocarbonyl)-3-thiazolidinyl]methyl]-3-methylbutyl]-L-histidinamide]-, [R-(R*,S*)]- (9CI) (CA INDEX NAME)
NTE modified (modifications unspecified)

type	------ location ------		description
stereo	Phe-1	-	D

SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 123:112728

REFERENCE 2: 123:9930

L23 ANSWER 25 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 142828-01-1 REGISTRY
CN Ranatensin, 1-de(5-oxo-L-proline)-2-de-L-valine-3-D-phenylalanine-10-[N-(3-aminopropyl)-L-leucinamide]-11-de-L-methioninamide- (9CI) (CA INDEX NAME)
NTE modified
SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 117:83809

L23 ANSWER 26 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 130832-65-4 REGISTRY
CN Ranatensin, 1-de(5-oxo-L-proline)-2-de-L-valine-3-(4-chloro-D-phenylalanine)-10-(N-butyl-L-leucinamide)-11-de-L-methioninamide- (9CI) (CA INDEX NAME)
NTE modified

type	------ location ------		description
modification	Phe-1	-	chloro<Cl>

SQL 8

FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 114:673

L23 ANSWER 27 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 130800-39-4 REGISTRY
CN Ranatensin, 1-de(5-oxo-L-proline)-2-de-L-valine-3-D-phenylalanine-10-L-leucine-11-de-L-methioninamide-, ethyl ester (9CI) (CA INDEX NAME)
NTE modified
SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 123:306760

REFERENCE 2: 120:23724

REFERENCE 3: 119:86775

REFERENCE 4: 117:164325

REFERENCE 5: 114:673

L23 ANSWER 28 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 130800-38-3 REGISTRY
CN L-Leucine, D-phenylalanyl-L-glutaminyl-L-tryptophyl-L-alanyl-L-valylglycyl-L-histidyl-, methyl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ranatensin, 1-de(5-oxo-L-proline)-2-de-L-valine-3-D-phenylalanine-10-L-leucine-11-de-L-methioninamide-, methyl ester
OTHER NAMES:
CN 6-13-[D-Phe6]-Bombesin methyl ester
NTE modified
SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 131:179925

REFERENCE 2: 131:83232

REFERENCE 3: 130:33276

REFERENCE 4: 129:104499

REFERENCE 5: 126:42790

REFERENCE 6: 123:306760

REFERENCE 7: 122:256743

REFERENCE 8: 122:178898

REFERENCE 9: 121:4222

REFERENCE 10: 119:109435

L23 ANSWER 29 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 130800-37-2 REGISTRY
CN L-Leucine, D-phenylalanyl-L-glutaminyl-L-tryptophyl-L-alanyl-L-valylglycyl-L-histidyl-, hydrazide (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ranatensin, 1-de(5-oxo-L-proline)-2-de-L-valine-3-D-phenylalanine-10-L-leucine-11-de-L-methioninamide-, hydrazide
NTE modified
SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 131:83232

REFERENCE 2: 114:673

L23 ANSWER 30 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 130800-36-1 REGISTRY
CN L-Leucinamide, N-[3-methyl-2-[[N-[N-(N2-D-phenylalanyl-L-glutaminyl)-L-tryptophyl]-L-alanyl]amino]butyl]glycyl-L-histidyl-N-propyl-, (S)- (9CI) (CA INDEX NAME)
NTE modified

type	------ location ------		description
modification	Val-5	-	undetermined modification

SQL 8
FS PROTEIN SEQUENCE
SQL 8

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 114:673

L23 ANSWER 31 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 130800-31-6 REGISTRY
CN Ranatensin, 1-de(5-oxo-L-proline)-2-de-L-valine-3-D-phenylalanine-10-[N-[2-(4-methylphenyl)ethyl]-L-leucinamide]-11-de-L-methioninamide- (9CI) (CA INDEX NAME)
NTE modified
SQL 8

FS PROTEIN SEQUENCE; STEREOSEARCH
SQL **8**

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 114:673

L23 ANSWER 32 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 130800-30-5 REGISTRY
CN Ranatensin, 1-de(5-oxo-L-proline)-2-de-L-valine-3-D-phenylalanine-10-[N-(2-phenylethyl)-L-leucinamide]-11-de-L-methioninamide- (9CI) (CA INDEX NAME)
NTE modified
SQL **8**
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL **8**

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 114:673

L23 ANSWER 33 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 130800-29-2 REGISTRY
CN Ranatensin, 1-de(5-oxo-L-proline)-2-de-L-valine-3-D-phenylalanine-10-(N-heptyl-L-leucinamide)-11-de-L-methioninamide- (9CI) (CA INDEX NAME)
NTE modified
SQL **8**
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL **8**

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 114:673

L23 ANSWER 34 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 130800-28-1 REGISTRY
CN 3-10-Ranatensin, 3-D-phenylalanine-10-(N-hexyl-L-leucinamide)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ranatensin, 1-de(5-oxo-L-proline)-2-de-L-valine-3-D-phenylalanine-10-(N-hexyl-L-leucinamide)-11-de-L-methioninamide-
NTE modified
SQL **8**
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL **8**

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 131:83232

REFERENCE 2: 130:33276

REFERENCE 3: 114:673

L23 ANSWER 35 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 130800-27-0 REGISTRY
CN Ranatensin, 1-de(5-oxo-L-proline)-2-de-L-valine-3-D-phenylalanine-10-(N-butyl-L-leucinamide)-11-de-L-methioninamide- (9CI) (CA INDEX NAME)
NTE modified
SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 119:86775

REFERENCE 2: 114:178480

REFERENCE 3: 114:673

L23 ANSWER 36 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 124199-91-3 REGISTRY
CN L-Leucinamide, D-phenylalanyl-L-glutaminyl-L-tryptophyl-L-alanyl-L-valylglycyl-L-histidyl-N-propyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ranatensin, 1-de(5-oxo-L-proline)-2-de-L-valine-3-D-phenylalanine-10-(N-propyl-L-leucinamide)-11-de-L-methioninamide-
OTHER NAMES:
CN 3-10-Ranatensin, 3-D-phenylalanine-10-(N-propyl-L-leucinamide)-
NTE modified
SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 131:83232

REFERENCE 2: 130:33276

REFERENCE 3: 129:104499

REFERENCE 4: 126:42790

REFERENCE 5: 123:306760

REFERENCE 6: 122:256743

REFERENCE 7: 119:241685

REFERENCE 8: 119:109435

REFERENCE 9: 117:164325

REFERENCE 10: 116:129652

L23 ANSWER 37 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 124199-90-2 REGISTRY
CN 3-10-Ranatensin, 3-D-phenylalanine-10-(N-ethyl-L-leucinamide)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ranatensin, 1-de(5-oxo-L-proline)-2-de-L-valine-3-D-phenylalanine-10-(N-ethyl-L-leucinamide)-11-de-L-methioninamide-
NTE modified
SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 133:198647

REFERENCE 2: 127:288296

REFERENCE 3: 127:257832

REFERENCE 4: 126:42790

REFERENCE 5: 125:105528

REFERENCE 6: 123:306760

REFERENCE 7: 122:256743

REFERENCE 8: 121:74504

REFERENCE 9: 120:96458

REFERENCE 10: 120:23724

L23 ANSWER 38 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 124199-86-6 REGISTRY
CN Ranatensin, 1-de(5-oxo-L-proline)-2-de-L-valine-3-(4-chloro-D-phenylalanine)-10-L-leucinamide-11-de-L-methioninamide- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN BIM 26182
NTE modified

type	------ location ------		description
terminal mod.	Leu-8	-	C-terminal amide
modification	Phe-1	-	chloro<Cl>

SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 117:225864

REFERENCE 2: 112:132551

L23 ANSWER 39 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 124176-13-2 REGISTRY
CN Ranatensin, 1-de(5-oxo-L-proline)-2-de-L-valine-3-D-phenylalanine-10-L-leucine-11-de-L-methioninamide- (9CI) (CA INDEX NAME)
SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 115:150746

REFERENCE 2: 112:132551

L23 ANSWER 40 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 124176-08-5 REGISTRY
CN Ranatensin, 1-de(5-oxo-L-proline)-2-de-L-valine-3-(N-acetyl-D-phenylalanine)-10-L-leucinamide-11-de-L-methioninamide- (9CI) (CA INDEX NAME)
NTE modified

type	------ location ------		description
terminal mod.	Phe-1	-	N-acetyl
terminal mod.	Leu-8	-	C-terminal amide

SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 115:150377

REFERENCE 2: 113:172755

REFERENCE 3: 112:132551

L23 ANSWER 41 OF 41 REGISTRY COPYRIGHT 2001 ACS
RN 124176-07-4 REGISTRY
CN 3-10-Ranatensin, 3-D-phenylalanine-10-L-leucinamide- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ranatensin, 1-de(5-oxo-L-proline)-2-de-L-valine-3-D-phenylalanine-10-L-leucinamide-11-de-L-methioninamide-
OTHER NAMES:
CN [D-Phe6]bombesin(6-13)NH2
NTE modified

type	------ location ------		description
terminal mod.	Leu-8	-	C-terminal amide

SQL 8
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 8

SEQ 1 FQWAVGHL
========
HITS AT: 1-8

REFERENCE 1: 131:83232

REFERENCE 2: 130:33276

REFERENCE 3: 123:306760

REFERENCE 4: 118:205226

REFERENCE 5: 116:716

REFERENCE 6: 115:150377

REFERENCE 7: 114:178480

REFERENCE 8: 114:673

REFERENCE 9: 113:172755

REFERENCE 10: 112:132551